Impact of a detailing restriction policy on prescription behavior

PhD in Management

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PhD Student: António José Carreira Valente | Nr. 50036599

Advisõrs: Professor Irina Saur-Amaral

Professor Fernando Gonçalves

Thesis specially prepared in order to obtain a doctorate degree. The opinions expressed strictly represent those of the author

Author's declaration of originality

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30th of June 2020

To Maria and António

My love for my little astronauts is bigger than the diameter

of Jupiter and more intense than the beauty of Neptune

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Foreword – PhD thesis journey: a personal reflection

The motivation to start a PhD in management ignited at the final stage of my MSc thesis development, in the sequence of the conclusion of my MBA, more than 10 years ago. However, the professional career at Cegedim and then at IMS Health, on top of the lecturing activities I developed until 2015, left little space for such a demanding endeavor.

In 2015 I decided to stop my lecturing activities and started searching for potential areas for research, from both a scientific point of view (by searching for articles on pharmaceutical marketing) and a pragmatic, industry practice point of view (which issues pharmaceutical companies face in the scope of pharmaceutical marketing and promotion investment decisions). Then, at around March-April 2016 I decided to enroll in this PhD program, the one that excited me the most given the intense curricular component (one full year of classes with ten subjects, divided in two semesters, and four additional semesters with regular research seminars).

After the first months of classes the perimeter of research started to become more circumscribed, in the topic of detailing and regulation of promotion activities. Then, with the assistance of my supervisor, we defined the final topic of research, based on future research suggestions from Stremersch & Van Dyck (2009) and Liu, Gupta, Venkataraman & Liu (2016): the impact of a detailing ceiling on physician prescription behavior. This topic was defended through one semester of plenary sessions with senior professors, and later was formalized in a thesis project.

During the first 15 months of the program my dedication to the PhD was set at around 50%, where the other 50% were dedicated to consulting activies. During this stage, I finished the curriculum component, finished and defended the thesis project, did most of the literature review, and took the opportunity to meet with several pharmaceutical industry officers and consultants, to gain critical insights and have access to the dataset (several meetings with IQVIA officers).

Then at the end of December 2017, I was invited by my current employer - Cegedim – to help launch a new business unit in Spain. After a period of reflection, I accepted the challenge and started working in Barcelona in May 2018, from Mondays to Thursdays, leaving Fridays to continue my research, in Portugal, where my family stayed. The intensity of 100+ flights per year and overall logistics (subway, train, taxi, and bags) was a challenge but did not provoke a substantial impact on my PhD research activities, other than less sleep hours than needed.

My research week typically started on Mondays after work and after some weekly shopping in Barcelona, where with luck I was able to dedicate two hours to my thesis. The most efficient days were typically Tuesdays and Wednesdays, where I was able to study at least three hours per night. Fridays were dedicated to consolidate the research developed in the previous days, to meet with my supervisors, and to advance in new research topics. Saturdays and Sundays were typically dedicated to my family, but in periods of higher pressure and need for concentration I went to Universidade Europeia to study, especially during the morning.

I started my quantitative research (data preparation) during the first quarter of 2018, merging two databases (sales and promotion investments), whose process seemed endless given the high number of products (18) and the need to create new variables (such as for instance sales in DDDs). This was a huge, very heavy process.

After this process, I started applying the quantitative models to the time series, which was, again, an incredibly dense phase, given the high number of products, the high number of models applied, and the unexpected high number of issues detected with our data (multicollinearity in some models mainly due to interaction variables, and other). With the enthusiasm of applying previous models developed by other researchers and the curiosity of testing adapted ones we reached 11 models, way more than expected a few months before. During quarter three 2018 I consolidated the quantitative phase and performed the series break test, after a number of meetings with my co-supervisor. However, during a problem with heteroscedasticity with two products, I had to get back to the quantitative phase in July and August 2019, to fine tune Model 8.4 and run the Chow test again for these products, this time using the software Eviews.

Going back to the end of 2018, and now with the global preliminary conclusions of the quantitative phase, it was time to develop the case study protocol including the qualitative script, which was finalized in the middle of December 2018. The interviews had to be scheduled to Fridays or Saturdays only, in Portugal (given my professional activity in Barcelona), and after a very intense period I was able to finish the last interview in March 2019.

Another very difficult process started, with the transcription of the interviews, but step by step this was accomplished, with effort, at the beginning of May 2019. The next step was to load

the transcriptions, sound files and other sources at NVivo, where two additional meetings were made with my supervisor, this time in Aveiro.

I always considered myself a tendentially quantitative person, but to my surprise the qualitative phase of my research gave me a colossal pleasure to evolve and complete, mainly the coding and content analysis to try to detect patterns, which provided clear and deep insights on a broader scope than the one typically provided by numbers only. This includes both endogenous and exogenous variables that affected the Portuguese pharmaceutical market.

The final step of the thesis was a surprise. Probably saturated with the work-research-travel-lack of sleep routine, I was not fully aware, before starting a two-week vacation period, of the level of completeness of my thesis, at that moment.

During those two weeks I had some restleness, almost always thinking "Instead of being here at the beach I should be finishing my thesis, maybe I won´t be able to observe the deadline". However, after these two weeks at the end of July 2019, and then at the beginning of August, I realized I had little to conclude, including the revision of the conclusions, the update of the discussion, the improvement of further research suggestions, the development of the limitations chapter, and then a deep validation of the whole document in prototype mode, before sending it to my supervisors on the 17th of August 2019. And at this final stage I remembered critical moments of my research:

- The moment I approached my supervisor at the University bar and she accepted to assist me during my PhD journey, and the moments while we revised my work and defined the next steps of the research. In my mind, Professor Irina is the Ultimate Thinking Machine, having the ability to find incredible science-based solutions for very demanding problems that seemed almost impossible to solve;
- The moment when I approached my co-supervisor asking for help after a stressful period at the beginning of the time series analysis, and he also accepted to assist me during my journey. During the many meetings Professor Fernando and I had, not only I learned about the critical issues of my thesis, but also about astronomy, astrophysics, human evolution, human intelligence, the evolution of species and the planet, and many other science-related themes;
- The moments when I received very negative feedback on my research topic idea, during a few of the plenary sessions – I arrived home thinking "I have been

researching this topic in the last six months and now it is not suitable for a PhD thesis?" But then, after a meeting with my supervisor, during which I asked for help (literally "Please help!"), and additional preparation and structuring of the ideas and slides, I was congratulated by the senior professors in the next session, keeping the research topic;

- The intense summer of 2017, where I most likely wrote 60 to 80 pages of my literature review, at the Public Library of Leiria;
- Intense Tuesdays and Wednesdays during the summer of 2018, during which I worked on my thesis from 05pm to 11pm at home (summer office schedule from 09am to 04pm, with no break), in Barcelona, at my living room heated by the sun up to 35 to 40 degrees Celsius, with no air conditioning, and very weak wind blowing;
- The moment I presented my work at ISPIM, in 2018, and the network I expect to keep and develop in the future;
- The moment I wrote this chapter, in August 2019, and realizing, with pride, that I was finishing my thesis
- And now, the moment I am finishing the amendments proposed by the jury members, in March 2020, in the middle of the alert state with Covid-19 virus, working remotely from home, in Portugal. Hopefully I may approach the public evaluation soon and be granted the PhD title in Management.

In my head, this journey makes me remember a very long train, one with 150+ cars representing the number of weeks of my research in these last three years, where I assumed -depending on the research phase -, different roles.

Sometimes I had to be the train driver, whenever I had to step on the accelerator and evaluate whether the railroad was clear to continue moving forward; other times I had to be the train engine, pulling hard even during montain railrods with incredible gradient, taking advantage of the engine torque (which I could rename as power of will and resilience, even after sleeping and drooling on the keyboard of my old companion – my laptop); other times I had to be the cars, taking advantage of the momentum of previous steps of the research, and leaving the ideas flow with no substantial effort (as for instance the final steps of the content analysis); and in other times I had to be the patient car driver waiting for the train to pass-by before crossing the road, such as for instance the periods when I was waiting for IQVIA's datasets, or the (short) periods while I was waiting for my supervisors feedback.

I am really glad I was part of this journey and that I had the possibility to learn and develop my scientific and personal skills. I am clearly a different (hopefully better) person after the PhD journey and I feel that the true scientific journey has hardly begun… I am looking forward to the next steps.

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List of Abbreviations and Acronyms

ABPI - Association of the British Pharmaceutical Industry

AIM - Autorização de Introdução no Mercado (Marketing Authorization)

AMA – American Marketing Association

ANF – Associação Nacional de Farmácias (National Association of Pharmacies)

APIFARMA - Associação Portuguesa da Indústria Farmacêutica (Portuguese Pharmaceutical Industry Association)

ARB - Angiotensin II Receptor Blocker

ATC - Anatomical Therapeutic Chemical

CAGR - Compound Annual Growth Rate

CDSS - Clinical Decision Support Systems

CLM – Closed Loop Marketing

CME – Continuous Medical Education

CNPR - Certified National Sales Representative

COPD - Chronic Obstructive Pulmonary Disease

CRM – Customer relationship management

DDD – Defined Daily Dose

DTC – Direct-to-consumer

DTCA – Direct-to-consumer advertising

EFPIA - European Federation of Pharmaceutical Industries and Associations

EMA – European Medicines Agency

ERS – Entidade Reguladora da Saúde (Health Regulation Entity)

FDA – Federal Drug Administration

GP – General Practitioner

HCO – Health Care Organization

HCP – Health Care Practitioner

HIO - Health Information Organization

INFOMED – Base de Dados de Medicamentos (Drugs database)

IMC – Integrated Marketing Communication

INE – Instituto Nacional de Estatística (National Statistics Institute)

INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (former Instituto Nacional da Farmácia e do Medicamento, I.P.) (National Drugs and Health Products Authority)

INN - International Nonproprietary Names

INTERFARMA - Associação da Indústria Farmacêutica de Pesquisa (Pharmaceutical Industry and Research Association)

IQR – Interquartile Range

KAM – Key Account Manager

KOL – Key Opinion Leader

LOE – Loss of Exclusivity

MNSRM – Medicamentos Não Sujeitos a Receita Médica (products not subject to medical prescription)

MSL - Medical Scientific Liaison

MSRM – Medicamentos Sujeitos a Receita Médica (products subject to medical prescription)

NAPSR - National Association of Pharmaceutical Sales Representatives

NHS – National Health System

OECD - Organization for Economic Co-operation and Development

OME – Other Marketing Expenditures

ONM - Ordre National des Medicins

OTC - Over-the-counter

PAAB - Pharmaceutical Advertising Advisory Board

PLACOTRANS - Plataforma de Comunicações - Transparência e Publicidade (Transparency Platform)

PhRMA - Pharmaceutical Research and Manufacturers of America

PMAC - Pharmaceutical Manufacturers Association of Canada

PSR – Pharmaceutical Sales Representative

ROI – Return on Investment

R&D – Research & Development

SFA – Sales Force Automation

SFE – Sales Force Effectiveness

SOV – Share of Voice

WHO – World Health Organization

Abstract

State of the art and research positioning

In the pharmaceutical industry, physicians control more than four fifths of health care expenditures, situation leading to a high investment of the pharmaceutical companies in marketing, aiming to influence phsyicians in their prescription behavior. Marketing-related factors influencing prescription behavior include detailing and detailing ceilings are a form of government-imposed regulation on companies' promotion. Counterfactual simulations made by previous researchers suggest that a detailing ceiling may have a negative effect on drugs sales. Our thesis focuses on the impact of detailing ceilings on physicians' prescription behavior, contributing to this stream of research.

Relevance and originality

We observe the call for research made by Stremersch & Van Dyck (2009) in studying policy experiments, by Wieringa & Leeflang (2013) in providing empirical analysis on an EU country, and by Liu et al (2016) in providing evidence on an area of scant research, therefore securing the relevance. Our research also contributes to the work performed by Larkin, Ang, Avorn & Kesselheim (2014) and Larkin et al (2017) by providing empirical results using data from a country that has restricted the access to physicians simultaneously to all institutions at a national level. It also contributes with the study of novel variables not studied in previous research. These aspects guarantee the originality.

Research question

Our research question is, therefore: *What is the impact of a detailing restriction policy on physicians' prescription behavior?*

Methodological approach

We used a mixed method approach, starting with a quantitative phase using a time series of drug sales and promotion investments (IQVIA). We used four models applied by Leeflang & Wieringa (2010) and applied seven other models to 18 products in four markets. We performed a series break test on detailing elasticities (before and after the ceiling). We then made 20 in-depth interviews with officers from the pharmaceutical market, to understand the quantitative results.

Results, conclusions and answer to the research question

Detailing is the most used promotion instrument and globally the preferred by physicians. Detailing flow is the most impactful instrument, but at a lower magnitude versus previous research. As the answer to our research question, our work did not find quantitative evidence to confirm the existence of changes in detailing flow elasticities before and after the entry into force of the 2013 detailing ceiling. The ceiling was apparently not fully implemented in all country, and its control varied substantially from region to region. Companies and PSRs used several tactics to mitigate the effect of the 2013 detailing ceilingin order to globally keep approximately the same call pressure on physicians.

Discussion

Our results globally adhere with previous theory on pharmaceutical marketing regarding the signals of the coefficients. However, they did not provide evidence to say that detailing elasticities were significantly different before and after the entry into force of ceiling. 20% of the drugs with the highests detailing intensity evidenced a reduction in detailing elasticity, and 71,4% of the drugs with the lowest detailing intensity evidenced an increase in detailing elasticity (but the results were not significant).

Contributions

We contribute to the theory by confirming previous research on detailing, and by generating specificities. Our research also contributes with the discovery of the inexistence of a significant statistical effect of the detailing ceiling on physician prescription behavior, which was not a result we would expect based on literature and raises questions about the effectiveness of the detailing ceiling policy. We studied novel, unique new variables in the scope of pharmaceutical marketing. We contribute to the practice, by allowing pharmaceutical companies a better understanding of the effect of several promotion tools on physician prescription behavior. We contribute to the policy by allowing the tutelage relevant insights on the application and control of Order 8213-B/2013, in the scope of public policy.

Limitations

We did not execute a systematic literature review of papers covering pharmaceutical marketing and regulation policy, and mainly searched literature in English. Our models – as the ones applied by Leeflang & Wiering (2010) did not evidence a substantial number of significant coefficients, and did not also pass all tests of good specification. We did not

interview young physicians and a more regional representation of some areas of the country would have allowed a higher representativeness.

Further research

Future investigations could address the effect of a detailing ceiling on competitive detailing, and study a ceiling impact on share-of-voice and on market share. Quantitative research in the scope of detailing ceilings in other countries or regions is also needed to understand whether this effect was due to the Portuguese context or due to the detailing ceiling policy per si. Further research on the implementation and control of nationally-wide detailing ceilings is welcome, especially in the sequence of an eventual adaptation of the Order. Further work can study more deeply the effect of exogenous variables in the evolution of medicines sales. The content and duration of pharmaceutical sales representatives (PSRs) calls and content should be studied.

Keywords – detailing, pharmaceutical promotion, prescription, detailing ceiling, pharmaceutical policy, lifesciences marketing

Palavras-chave – visita médica, promoção marketing farmacêutico, prescrição, limite visitas, política farmacêutica

1. Introduction

1.1.State of the art theoretical grounding

The current thesis is theoretically framed in the life sciences industry, specifically in the pharmaceutical industry, and in life sciences marketing, adopting the approach proposed by Stremersch & Van Dyck (2009).

The pharmaceutical industry presents several unique features when compared to other industries, especially consumer goods industry. While patients are the payers of the drugs (by their own money or through health insurance), they are not the deciders, since prescription medicines are chosen by physicians, who select a drug among a set of alternatives (Gönül et al, 2001), making prescription medicines market part of a captive market (Lexchin, 1997). The stakeholders who decide the product to prescribe, and to whom most promotional effort is directed, are not the purchasers, as underlined by Caplow & Raymond (1954). This industry is one of the most highly regulated ones by governments, aiming the protection of the health and well-being of the public (Handoo et al, 2012).

The life sciences marketing is, according to Stremersch & Van Dyck (2009) a novel, nascent field in marketing, offering opportunities for scholars to research its specific issues and unique challenging problems, using high-quality available data and that have a significant impact transcending the typical problems generally investigated by marketing researchers. The key marketing decision areas framework developed by Stremersch & Van Dyck (2009) offer a perspective of the main dimensions scholars and industry professionals may observe in their academic investigation and managerial practices, and consist of 1 - therapy creation, 2 - therapy launch, and 3 - therapy promotion. Therapy promotion comprehends sales force management, communication management, and stimulating patient compliance. Following Stremersch & Van Dyck (2009) framework, sales force management encompasses decisions on optimal sizing and targeting of the sales force, decisions that optimize sales call quality, and the optimization of the use of drug samples, including sales response models such as the impact of detailing on prescription behavior. Figure 1.1 evidences the theoretical pavement proposed by Stremersch & Van Dyck (2009).

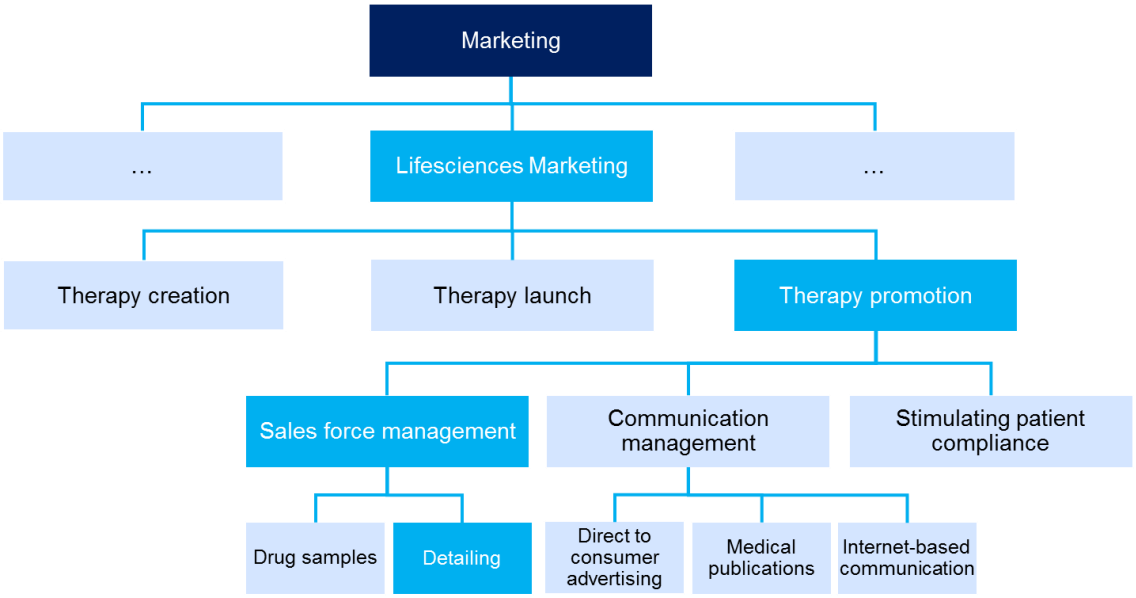


Figure 1.1 - Marketing of the Life Sciences

Source: adapted from Stremersch & Van Dyck (2009)

Pharmaceutical manufacturers use, in the scope of their sales force management, sales force teams consisting of pharmaceutical sales representatives (PSRs), also called reps (Caplow & Raymond, 1954), who provide education and information to physician offices, hospitals, pharmacies, and other healthcare providers (Alkhateeb et al, 2011), acting as important marketing and sales instruments (Scharitzer & Kollarits, 2000), and trying to influence physicians to increase the promoted drugs sales (Fugh-Berman & Ahari, 2007). Their job is to introduce and market their companies' products, using, in the interaction with physicians, several promotion instruments such as free drug samples, gifts, free meals and sponsorships (Salmasi et al, 2016).

Physicians are health care professionals who have the statutory authority to prescribe prescription drugs, and consequently are the main deciders in the buying decision process (Gönül et al, 2001). Given their ability to write drug prescriptions, physicians control more than four fifths of health care expenditures, by prescribing or recommending products to their patients (Weeks, Wallace & Kimberly, 2001).

Several factors can influence physicians' prescribing behavior, and they may be marketing or non-marketing related.

Non-marketing related factors include physician and profession (Cialdini, 1984; Pitt & Nel, 1988; Roughead, Harvey & Gilbert, 1998; Coscelli, 2000; Spiller & Wymer, 2001; Campo et

al, 2006; Moynihan, 2008; Meffert, 2009; Katz, Caplan & Merz, 2010; Stros & Lee, 2015), market (Kalyanaram, 2008; Kremer et al, 2008), regulatory and institutional (Spiller & Wymer, 2001; Huskamp, Epstein & Blumenthal, 2003; Schumock et al, 2004; Kravitz et al, 2005; Aronson, 2006; Andersson, Petzold, Allebeck & Carlsten, 2008; Stremersch & Lemmens, 2009; Fischer, Koch, Kostev & Stargardt, 2017; King & Bearman, 2017), and patients (Mintzes et al, 2002; Kravitz et al, 2005 ; Campo et al, 2006).

Marketing-related factors include product (Pitt & Nel, 1988; Gönül et al, 2001; Schumock et al, 2004; Stros & Lee, 2015), promotion (Parsons & Abeele, 1981; Pitt & Nel, 1988; Berndt, Bui, Reiley & Urban, 1996; Spiller & Wymer, 2001; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004; Schumock et al, 2004; Kravitz et al, 2005; Chimonas, Brennan & Rothman, 2007; Gönül & Carter, 2009; Fugh-Berman & Ahari, 2007; Katz, Caplan & Merz, 2010; Stros and Lee, 2015; DeJong et al, 2016; King & Bearman, 2017), pricing / cost (Pitt & Nel, 1988; Gönül et al, 2001; Spiller & Wymer, 2001; Stros & Lee, 2015), and distribution (Pitt & Nel, 1988; Dimaculangan, 2011; Stros & Lee, 2015).

Pharmaceutical promotion - which Stros & Lee (2015) considered the marketing instrument that appears to be considerably more relevant than price, product of place – is generally limited to drugs on patent (Datta & Dave, 2016), and is one of the focus of this thesis. Pharmaceutical manufactures use communication channels (personal and non-personal, traditional and digital) and promotion tools (commercial and non-commercial, push and pull) to interact with physicians.

Detailing – a face-to-face meeting where PSRs present information to physicians (Molloy et al, 2002) – is the promotion tool with the higher investment by pharmaceutical manufacturers (Yi, Anandalingamb & Sorrell, 2003; Gagnon & Lexchin, 2008; Datta & Dave, 2016), and the promotion tool with the stronger impact on physicians' prescribing behavior (Pitt & Nel, 1988; Berndt, Bui, Reiley & Urban, 1996; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kalyanaram, 2008; Kremer et al, 2008; Kalyanaram, 2009; Dave & Saffer, 2012). It is a form of personal selling (Fischer & Albers, 2010), and a form of relational marketing (Gronroos, 1994). Its effect on physician prescribing behavior is on average significant, and positive (Kremer, Bijmolt, Leeflang & Wieringa, 2008), but modest (Stremersch & Van Dyck, 2009; Stremersch & Lemmens, 2009).

Many European countries, with the goal of reducing the pressure on public health care expenditures, developed initiatives to regulate the pharmaceuticals markets (Eger & Mahlich,

2014). One of the forms of regulation is to limit the pharmaceutical manufacturers' marketing practices, which can be self-imposed (Norris, Herxheimer, Lexchin & Mansfield, 2005; Francer et al, 2014), or government imposed (Stremersch & Lemmens, 2009). Government imposed regulation of marketing efforts to physicians has been addressed by several scholars including Brotzman & Mark (1992), Brotzman & Mark (1993), Wazana (2000), Brennan et al (2006), Liu et al (2016), and Karas, Bandari, Browning, Jacobs & Davies (2016), and have been demonstrated to have a negative effect on drug sales.

The restriction on the number of detailing visits a manufacturer can make, in a given period of time – also called detailing ceiling (Liu et al, 2016; Liu, Liu & Chintagunta, 2017) is the form of regulation which will be more deeply addressed in our thesis. Despite the scant literature on this specific field, existing evidence suggests that constraining the number of detailing visits a pharmaceutical company can make can lead to a negative effect on the sales of the promoted drugs (Stremersch & Lemmens, 2009).

This impact can be differentiated among drugs brands, as noted by Liu et al (2016). They estimated that, with a detailing ceiling, the drug with the largest detailing frequency suffers the most in terms of market share and profit decreases, while less detailed brand drugs appear to gain market share and profits, which suggests that a detailing ceiling may impact detailing elasticities differently among competing drug brands.

We analyzed precisely the effect, on detailing flow elasticities and therefore physician prescription behavior -, of the entry into force of a detailing ceiling in Portugal in 2013 through Order8213-B, to conclude whether it had any significant effect on the slope of the relation between detailing efforts and drug sales (using a Chow (1960) test, to search for eventual breaks in the time series).

1.2.Research positioning

The previous paragraphs presented the theoretical state-of-the-art grounding for detailing, its impact on physician prescription behavior, and the effect of a detailing ceiling on this impact.

Based on the articles selected for the literature review, and in order to properly define our research positioning in the pharmaceutical marketing community, we analyzed the type of research method used by previous researchers studying detailing and its effect on physician prescription behavior. We created three groups: one group with articles using time series, with a list of 44 articles; one group using cross-sectional research or experiments, with eight articles; and one group using qualitative research, with seven articles. The 44 articles using

time series will later be deeply analyzed, through a table characterizing the methods used, the variables analyzed, and the outcomes obtained in each article.

Table 1.1, table 1.2 and table 1.3 below evidence the main journals, impact factor and number of citations of articles in each of the groups.

Table 1.1 – Characterization of articles addressing detailing using a time series approach

Journal	Nr of articles using quantitative research - time series	JCR Impact Factor 2016	Average number of citations (Google scholar, 08th February 2018)
Journal of Marketing	5	5,318	202
Journal of Marketing Research	4	3,654	131
Management Science	4	2,822	94
Marketing Science	6	2,123	96
Health Economics	2	2,301	40
Marketing Letters	2	1,818	80
Quantitative Marketing and Economics	2	1,333	21
Expert Systems with Applications	1	3,928	10
Journal of Political Economy	1	3,923	44
Social Science & Medicine	1	2,797	37
Technological Forecasting and Social Change	1	2,625	7
Journal of Advertising Research	1	2,034	1
International Journal of Research in Marketing	1	1,775	49
Health care management science	1	1,419	13
Applied Economics	1	0,648	7
The Journal of Law and Economics	1	N/A	227
Forum for Health Economics & Policy	1	N/A	227
The Economics of New Goods	1	N/A	159
HBS Marketing Research	1	N/A	107
Association of Medical Publications	1	N/A	56
Southern Economic Journal	1	N/A	52
International Journal of Pharmaceutical and Healthcare Marketing	1	N/A	25
Managerial and Decision Economics	1	N/A	27
International Journal of Pharmaceutical and Healthcare Marketing	1	N/A	25
SSRN Electronic Journal	1	N/A	15
Harvard Business Review (working paper)	1	N/A	0

Note that 25 out of the 44 articles (or 57%) using time series approaches were published in top journals with a strong impact factor (weighted average of 3,05), and a high number of citations (weighted average of 110).

Table 1.2 – Characterization of articles addressing detailing using cross-sectional research or experiments

Articles on detailing and its effects on physician prescription behavior in the literature review perimeter

Journal	Nr of articles using qualitative research	JCR Impact Factor 2016	Average number of citations (Google scholar, 08th February 2018)
Annals of Internal Medicine	1	17,135	6
Journal of General Internal Medicine	1	3,701	141
British Journal of General Practice	1	2,760	66
Family Practice	1	1,804	70
Health Marketing Quarterly	1	N/A	46
Marketing Intelligence & Planning	1	N/A	1
International Journal of Pharmacy Practice	1	N/A	0

Having as a reference the articles selected for the literature review, only eight of them were identified as using either cross-sectional research (with questionnaires to physicians) or experiments (such as randomized control trials).

Table 1.3 - Characterization of articles addressing detailing using a qualitative approach

Articles on detailing and its effects on physician prescription behavior in the literature review perimeter

Journal	Nr of articles using quantitative research - cross-sectional /	JCR Impact Factor 2016	Average number of citations (Google scholar, 08th February 2018)
Schizophrenia Research	1	3,986	9
British Journal of Clinical Pharmacology	1	3,493	18
European Journal of Clinical Pharmacology	1	2,902	49
Annals of Pharmacotherapy	1	2,748	109
The European Journal of Public Health	1	2,431	56
European Journal of Marketing	1	1,333	37
Health Marketing Quarterly	2	N/A	38

Also having as a reference the articles selected for the literature review, seven of them were identified as using qualitative research.

In terms of research positioning in the community studying pharmaceutical marketing, this thesis will be framed, in the first phase, into previous quantitative research conducted by scholars using time-series data addressing detailing investments and drug prescriptions (or sales).

The first reason is the impact factor of the journals where previous research was published. As a second reason, the substantially higher number of articles using quantitative research, as opposed to qualitative research. Previous authors using the same research positioning include Gönül, Carter, Petrova & Srinivasan (2001), Narayanan, Manchanda & Chintagunta (2003), Manchanda & Chintagunta (2004), Mizik & Jacobson (2004), Manchanda, Rossi & Chintagunta (2004), Narayanan, Manchanda & Chintagunta (2005), Kalyanaram (2009), Leeflang & Wieringa (2010), Wieringa & Leeflang (2013), Ruiz-Conde, Wieringa & Leeflang (2014), Montoya, Netzer & Jedidi (2010), Datta & Dave (2016), and Liu et al (2016), to list a few.

Third, the fact that research addressing detailing restriction policies, disclosure and regulation of direct-to-physician promotion activities has been gaining momentum, evidencing a growing dynamic as an area of interest in the research community, such as contributions from Stremersch & Lemmens (2009), Stremersch & Van Dyck (2009), Grande (2009), Alkhateeb et al (2011), Liu et al (2016), and Karas et al (2016), to highlight a few.

Fourth, the fact that the quantitative research on pharmaceutical marketing is essentially circumscribed in the first group of articles, which is critical given that the current document is a thesis in Marketing. Despite the main focus being on quantitative research, we also performed a qualitative phase, to gain additional insights and help explain the results obtained with the quantitative phase.

1.3.Research question: Relevance and originality

The research question was set at the end of the literature review process, in the sequence of the analysis of the future research avenues of existing research on pharmaceutical marketing, promotion instruments and regulation policy.

The research question is:

- *What is the impact of a detailing restriction policy on physicians' prescription behavior*

Therefore, we argue that detailing ceiling policy has an impact on the prescription behavior of physicians (measured at the magnitude of the detailing flow elasticities), and this constitutes our thesis.

Detailing impact on prescription behavior has been studied in the last decades, mostly using US–based data, and especially since the 2000s. Some countries have started to set policy

restrictions on pharmaceutical sales representatives' access to physicians. Others are considering establishing such restrictions, as underlined by Stremersch & Van Dyck (2009). They suggested, as future research, the «*development of models that allow for policy experiments (…) all models are estimated on data that show relatively little policy variance, which inhibits any extrapolation to policy shifts in detailing, either by the manufacturer /…) or by the regulator*» (p. 13).

Stros and Lee (2014) – who addressed the persistent rise of costs in the health sector – also stressed the need to implement policies «*to reduce the high level of promotional influence on prescribers by inhibiting the companies' promotional activities*» (p. 330), while Wieringa & Leeflang (2013) asked for additional contributions to build empirical evidence whether the European pharmaceutical market is less or more responsive to marketing efforts than the US market.

Liu et al (2016) developed research on the impact of simulated detailing restriction policies on prescription behavior and competitive detailing using counterfactual simulations from structural equations. They pointed to the importance of the study of the impact of detailing restriction policies, stressing that «*(…) scant scholarly research has investigated how these restrictions on physician access impact physician prescription behavior and competitive detailing to physicians*» (p. 2), and that «*findings from counterfactual simulations provide rich implications for regulators and the pharmaceutical industry*» (p. 18). All these calls for future research support the **relevance** of our research.

Larkin, Ang, Avorn & Kesselheim (2014), when studying the impact of restriction of detailing activities in academic medical centers, found that a detailing restriction negatively impacts the market share of promoted drugs, and positively impacts the market share of nonpromoted drugs (antidepressants and antipsychotics in children). Three years later in a new article, Larkin et al (2017) found that detailing restriction policies had a modest but significant impact on physician prescription behavior (resulting in a reduction of on average 1,67 percentage points in the market share of the detailed drug) in six of the eight drug classes studied, and in eight of the 11 academic medical centers who implemented detailing restriction policies.

These two articles are recent contributions to the theory on detailing and restriction policies. However, they did not explicit whether the magnitude of the detailing restriction policy changed from center to center, only referring that it consisted of a regulation of salesperson

access to facilities. The extent to which the access had been limited (from a light access restriction to a full PSR ban in the centers facilities), might potentially have added additional insights on this research and magnify its generazability. They also lack the impact on competitive detailing, that is, how is the detailing dynamics affected by the entry into force of the policy restrictions (do all brands reduce their detailing efforts? Do the brands increase the usage of alternative promotion investments?).

To the best of our knowledge, no additional research has been developed meanwhile, giving room to the analysis of the impact of detailing policy restrictions on prescription behavior, using data from a country – Portugal – that has actually set restriction access to physicians for detailing purposes, simultaneously to all institutions at a national level (Order 8213–B/2013 imposed a detailing ceiling, setting limits to the number of visits pharmaceutical sales representatives can make to physicians and in each national health system infrastructure).

In terms of research objectives, we divided in general and specific goals, associated to the research question:

- General objective – Determine the impact of a detailing ceiling on physician prescription behavior
- Specific objectives
    - Assess the relation between detailing flow and drug prescriptions
    - Assess the patterns of this relation among different therapeutic classes (markets) and products typologies
    - Assess the extent to which previous quantitative models are adequate to a Portuguese pharmaceutical industry dataset
    - Evaluate whether the moderating effect of a detailing ceiling negatively affect detailing flow elasticities
    - Generate a broader, holistic understanding of the Portuguese pharmaceutical market and the dynamics of the implementation of a detailing ceiling

Our research adapts previous quantitative models to the Portuguese reality (models 8.1 to 8.4), also using novel variables not studied in previous research, such as the effect, on physician prescription behavior, of the number of products presented during the calls, the percentage of calls where physicians declared they would increase or start prescribing the detailed product, the use of printed materials during the call, and the use of tablets during the

call. Our research also explores detailing elasticities in a new class – which we called "Blood" (respecting the request made by IQVIA for anonymity of classes and products) -, comprising very expensive recent drugs that noticed a substantial growth in terms of sales, and which represents, growingly from 2011-2012, a big burden on NHS budget.

We argue that our thesis is the first work performed using a mixed method approach in the same research, to help understand the quantitative results in light of the specific market, social, economical and regulatory reality of the country and pharmaceutical industry, involving more than 20 participants from different stakeholders (pharmaceutical sales representatives, physicians, high officers from the NHS tutelage, NHS health care organizations, and pharmaceutical companies, physicians, and consultants). We argue it is the first time the effect of a nationally implemented detailing ceiling and its impact on physician prescription behavior is measured using both quantitative and qualitative data, and the first time the implementation and control of a detailing ceiling is addressed, to the best of our knowledge. All these aspects support the **originality** of our research.

With our research, by analyzing the impact of a detailing restriction policy on detailing flow elasticities of several drugs, we argue that we generated not only quantitative robustness, but also qualitative uniqueness by exploring the quantitative results using a mixed method approach.

1.4.Methodological approach

1.4.1. Literature review

In the scope of the literature review of the state-of-the-art theories, EBSCO and b-on databases were used for articles search, using the following keywords: pharmaceutical marketing, pharmaceutical promotion, detailing and prescription, pharmaceutical regulation, detailing restriction policies.

In a first moment, 123 articles were selected and abstracts were extracted and compiled into a single database in word processor format (DOC), with a balanced selection of less recent and more recent articles. The reading of these abstracts allowed a first understanding of the main concepts addressed by previous researchers in the pharmaceutical marketing and regulation and policy fields, and the most used methods for data analysis (quantitative using time series, quantitative using cross-sectional research, and qualitative using in-depth interviews and

focus groups). A special attention was given to the future research suggestions given by the scholars.

As the literature review was developed, other references were extracted, adding articles from journals with high impact factors; articles with a substantial amount of citations; and articles often referenced by the most active researchers in this field.

A special attention was given to the time horizon of the publication date, including as far as possible articles from 1980 to 2019, allowing the study of not only the historical references in this field, but also of more contemporaneous research.

This process resulted in a final perimeter of 289 peer-reviewed articles analyzed. In the literature review process, we also analyzed a selection of 146 non-peer reviewed sources including pharmaceutical industry associations' reports, pharmaceutical companies' websites and reports, consulting companies' reports, national health system legislation and reports, white papers from experts, reference books, and other, many of which cited in peer-reviewed articles (for instance, IQVIA syndicated data regarding medicines sales, promotion investment magnitude, and other).

1.4.2. Research variables

The performed literature review allowed the identification of the conceptual model, or theoretical pavement that permits the identification of the main variables involved, forming a research hypothesis, which specifies the relationship among variables in terms of direction (Creswell, 2014). The dependent variable is sell-in sales (measured as Ln Drug sales), the independent variable is the detailing intensity (measured as Ln Detailing flow), and the moderating variable is the policy measure consisting of the 2013 detailing ceiling (Order 8213-B/2013). A visual representation of the conceptual model is presented below, in figure 1.2, here adapted from Liu et al (2016)' research.

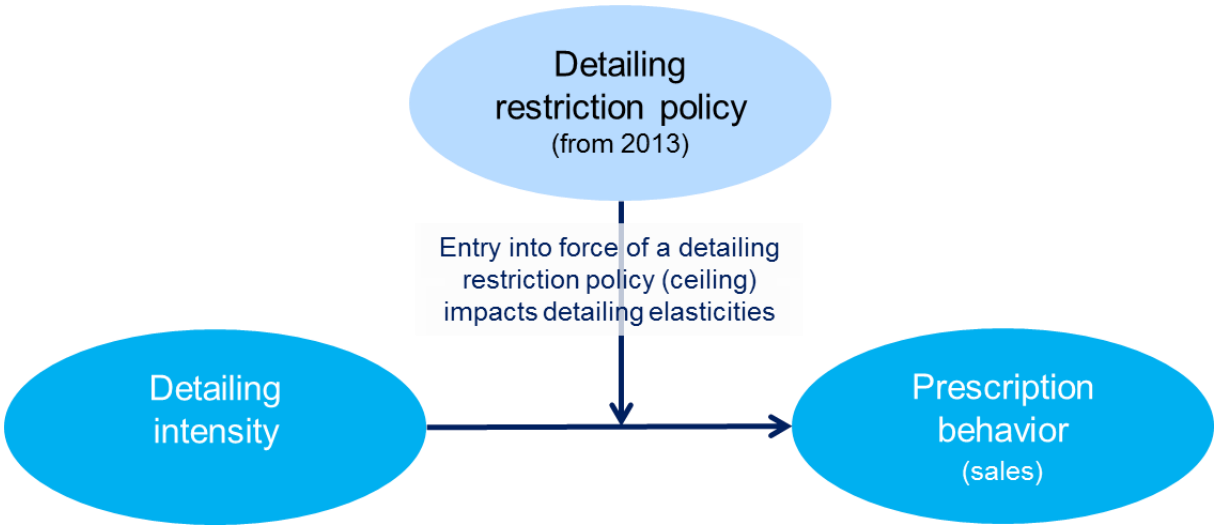


Figure 1.2 – Conceptual model

Source: adapted from Liu et al (2016)

1.4.3. Empirical study

The empirical study observed a mixed research method, using a sequential explanatory design.

The selection of this research approach was based on four main reasons: the search for comprehensiveness, as highlighted by O'Cathain, Murphy & Nicholl (2007), engaging with the «*complexity of health, health care interventions, and the environment in which studies took place*» (p. 85); a better understanding of the research problem «*by converging broad numeric trends from quantitative research, and the detail of qualitative research*», as underlined by Creswell (2009, p. 121); a more detailed understanding of the data by «*using qualitative follow–up data to help explain a quantitative database*», as pointed by Creswell (2014, p. 177); and the fact that «*qualitative research may facilitate the interpretation of the relationship between variables*», as suggested by Bryman & Bell (2015, p. 653).

These last authors also underline the fact that «*quantitative and the qualitative data deriving from mixed research methods research should be mutually illuminating*» (p. 641), and that «*triangulation involves using more than one method or source of data in the study of social phenomena*» (p. 402).

In terms of sequence, the proposed research will observe the following steps:

Figure 1.3 - Research method approach

Source: adapted from Creswell (2009)

The research objective was explanatory in the first phase, studying the causal effect of the detailing activities on the prescription behavior through time and the moderating effect of a detailing ceiling, on detailing elasticities. The research objective was then exploratory in the second phase, to help understand the specific results from the quantitative phase. The research was correlational in the quantitative phase, using a posteriori control (there was no control in the qualitative phase). In terms of context, both research phases were classified as field (natural).

The selection of this research design (objective, control and context) for the quantitative phase was aligned with the designs used by the majority of the researchers in the pharmaceutical marketing community. These include (but not limited to) Fischer & Albers (2010), Liu et al (2016), Mizik & Jacobson (2004), Narayanan, Manchanda & Chintagunta (2003), Datta & Dave (2016), Gönül, Carter, Petrova & Srinivasan (2001), Kalyanaram (2009), Manchanda & Chintagunta (2004), Manchanda & Honka (2005), Montoya, Netzer & Jedidi (2010), Narayanan, Manchanda & Chintagunta (2005), and Riese et al (2015).

For the qualitative phase, aimed at exploring insights on the behavior of healthcare professionals including physicians, the research design was aligned with previous work conducted by authors like Grundy, Bero & Malone (2016), Prosser & Walley (2013a), Prosser & Walley (2013b), Saavedra, O'Connor & Fugh-Berman (2017), and Skandrani & Sghaier (2016).

The research used longitudinal data in the first phase, as observed by researchers in the pharmaceutical marketing community for quantitative research. A time series of drug sales and marketing investments was used (aligned with authors such as Fischer & Albers, 2010; Liu et al, 2016; Mizik & Jacobson, 2004; and Narayanan, Manchanda & Chintagunta, 2003). A data series of four years was used (19 months before the 2013 detailing restriction policy, and 29 months after), in order to analyze the impact of detailing on prescription behavior as

measured on detailing flow elasticities, before and after the entry into force of a detailing ceiling. The research was then cross–sectional in the second phase.

As we studied a specific European context (Portugal), we accounted for the fact that it has a very distinct reality regarding availability of prescription data, when compared to the USA. Physician-level prescription data is only available to SPMS (an institution in the perimeter of the NHS) and is not allowed, by law, for commercial purposes. Also, promotion data is only partially available to Infarmed through Placotrans, but at the moment we are writing this subchapter it is not organized and compiled properly, and misses the detailing activities (disclosure of detailing activities is not required).

Therefore, we used secondary data collected by IQVIA, an American consulting company that resulted from the merger of IMS Health and Quintiles, providing services to the pharmaceutical industry. IQVIA (or companies acquired by former IMS Health, such as Verispan / Scott Levin, and SDI Health) has been the main data provider for research in the pharmaceutical marketing community, providing data for authors that studied detailing, including (but not limited to) Chintagunta & Desiraju (2005), Dave & Saffer (2012), Datta & Dave (2016), Dong, Chintagunta & Manchanda (2011), Dong, Manchanda & Chintagunta (2009), among others. Primary research was generated in the second phase, by exploring the moderation effect of a detailing ceiling on the impact of detailing on physician prescription behavior).

The time series data IQVIA provided consisted of sales of eligible medicines through time, called sell–in data, defined as sales valued at the wholesale price (or price pharmacies pay to the wholesalers in the pharmaceutical marketing channels) – collected through agreements made with pharmaceutical wholesalers -, and promotion investments made by pharmaceutical companies (including detailing) – collected using a representative panel of physicians, whose data is extrapolated to the physician universes.

Information from the quantitative phase was explored further using one case study consisting of the Portuguese pharmaceutical industry, for triangulation of results. The actors included prescribers (physicians), influencers (pharmaceutical sales representatives), regulators, and others that helped understand specificities of the quantitative results. A case study protocol was developed and implemented. Data collection methods and tools used were semi-structured interviews, researcher observations, documental analysis, and non-structured interviews. Content analysis was made using NVivo 11.

1.5.Summary of results and conclusions

This sub-chapter presents summarized insights on the results and conclusions of our thesis, allowing a preview of Chapter 15, where the complete set of results and conclusion have been presented in detail.

After our research has been concluded, detailing remains the most used promotion instrument to interact with physicians, and generally the preferred one by physicians, especially more experienced ones, who tend to value the regular contact of PSRs and benefit from delivery of novelties and the prompt clarification of doubts. Detailing flow is on average the most impactful promotion instrument, with evidence coming both from the quantitative and qualitative steps of our research.

The effect of detailing appears, however, to be smaller versus the effect observed in previous studies mainly conducted in the USA. Detailing is especially impactful in the case of younger drugs, which is consistent with the fact that most companies invest more heavily in detailing activities during the first stages of the drugs lifecycle. Also, detailing reduces the price elasticity of drugs, especially in the case of younger drugs. By other words, detailing appears to immunize, to a certain extent, doctors' awareness and perception of drug price at the moment they prescribe a drug.

Detailing is not only important in the case of current investments: past investments made in detailing activities generally have a positive impact on drug sales (carry-over effects of detailing), again especially in the case of younger or much younger drugs, while physicians are more prone to receive information about novelties. Detailing initiatives performed by competitor brands, or competitive detailing, generally have a negative impact on the own promoted drug.

The usage of iPads / Tablets grew during the period of our analysis (2012-2015) and appears to bring positive effects to the sales of the promoted drugs, probably given the novelty effect of this new communication technology, with interactive screens. Physicians revealing more positive future prescription intentions regarding the promoted drugs are more likely to promote them. A high number of promoted drugs during a sales call may negatively impact the main drug promoted.

Most likely, Order 8213-B/2013 was not entirely implemented on a national basis, given the difficulty to control PSRs access to the NHS in a conjuncture of reduced administrative and security staff, and with no apparent audits from the tutelage.

The 2013 detailing ceiling had a higher effect during the first year, then losing effectiveness due to some decompression of the control, apparently absent to many of the interviewees. The North, Center, and high population regions apparently had a higher control than the South (Alentejo and Algarve) regions. Control is likely higher in certain political scenarios (in ACES). Pharmaceutical companies reacted to the ceiling mainly by increasing the investment in group sessions, in digital channels and promotion tools.

As seen in our quantitative phase with our time series, **Order 8213-B/2013 apparently did not provoke a structural change in physician prescription behavior measured through detailing flow elasticities, given that not one single product evidence significant changes in its elasticities, before and after the entry into force of this ceiling, which represents the main conclusion of our thesis**. At most, as addressed during the qualitative phase, it may have marginally impacted the beginning of the prescription of new medicines, less promoted in some NHS institutions**.** Much stronger than the detailing ceiling by itself are likely other measures including INN prescription, highly constraining prescription systems, expense ceilings, the economic crisis, Troika intervention, among other, who in fact created the ground for a new paradigm in the pharmaceutical industry, in Portugal.

1.6.Summary of contributions

This sub-chapter presents summarized insights on the contributions to the theory, to the practice, and to the public policy, allowing to preview the detailed presentation described in chapter 13.2.

Our research contributes to the theory with several insights to management and marketing, by confirming, by the one hand, previous research on detailing (Pitt & Nel, 1988; Berndt et al, 1995; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kalyanaram, 2008; Leeflang & Wieringa, 2010, and many others, and by the other hand generating new evidences such as for instance the stronger impact of detailing on price elasticities of younger versus older drugs (Rizzo, 1999; Gönül et al, 2001; Narayanan et al, 2004; Windmeijer et al, 2006), and the finding that detailing carry-over effect on drug sales is more intense in the case of younger drugs (generating additional insights on research conducted by Narayanan et al, 2004; Zoltners, Sinha & Lorimer, 2004; Yi, 2008; Montoya, Netzer & Jedidi, 2010; Liu et al, 2016). Our research also contributed by studying novel, fresh data in the study of pharmaceutical marketing and specifically detailing (building on previous research in the field of pharmaceutical marketing developed by authors such as Pitt & Nel; 1988; Berndt et al, 1995; Narayanan et al, 2003; Narayanan, Desiraju &

Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kalyanaram, 2008; Kremer et al, 2008; Kalyanaram, 2009; Dave & Saffer, 2012). Our research also contributed with the discovery of the inexistence of a significant statistical effect of the detailing ceiling on physician prescription behavior, which goes against previous theory developed by Brotzman & Mark (1992), Brotzman & Mark (1993), Liu et al (2016), Karas et al (2016), and Larkin et al (2017). It also evidenced that the detailing ceiling benefited from several exogenous variables impacting much more the number of PSRs and physicians' prescription behavior than the ceiling itself.

Our research also contributes to the practice, considering several stakeholders scopes. It allows pharmaceutical companies a better understanding of the effect of several promotion tools (including detailing) on physician prescription behavior, using a European database, allowing a better sales force effectiveness policy. They can also benefit from the understanding of the implementation and impact of a national detailing ceiling. Marketing departments can most efficiently calibrate their communication and promotion activities, in order to meet stakeholders' (especially prescribers) expectations. The new variables used in our research can provide critical insights for pharmaceutical and biotechnological companies in the scope of promotion and salesforce effectiveness. Associative institutions – such as APIFARMA – can benefit from the insights generated in our research, allowing them to be better prepared and backed by empirical evidence on the areas where the detailing ceiling may be improved. Physicians can benefit by confirming the existence, in several products analyzed, of a clear effect of detailing on prescription behavior, allowing doctors to become aware of this influence and be better equipped to interact with PSRs and the pharmaceutical industry in general.

Our research also contributes to the public policy. Policy makers may benefit from our research by a series of reasons. The first is the realization that detailing initiatives do impact physician prescription behavior in Portugal, especially in the case of more recent (and typically more expensive, and reimbursed) drugs. This evidence may raise the attention on the topic of pharmaceutical marketing in general, in a scenario of very constrained budgeted costs with medicines. The tutelage can also understand that the ceiling may have not been totally implemented and controlled, allowing the study and launch of eventual corrective measures. The tutelage can clearly benefit from analyzing the delicate equilibrium between the need to regulate PSRs' access to physicians and NHS HCOs, and the need to continue benefiting from

the pharmaceutical companies assistance in training, raising awareness on pathologies, and assisting doctors on a regular base.

1.7.Thesis structure

This document is organized in chapters, each one starting with the content and logic of the chapter, addressing the main concepts, exploring the state of the art knowledge, ending with a synthesis of the main findings to help systematize the existing knowledge, also helping later to develop the conceptual model.

Chapter two describes the main theories on the life science industry and life science marketing, providing the macro theoretical pavement for the development of the rest of the literature review.

Chapter three addresses sales force management in the pharmaceutical industry, highlighting theories on sales force effectiveness, customer relationship management and sales force automation, and pharmaceutical sales representatives.

Chapter four approaches the main theories on physicians (as the main professional class with prescription authority) and on medical prescription (and factors influencing it).

Chapter five analyzes pharmaceutical industry promotion, highlighting theories on communication channels, promotion tools (specially detailing), promotion tools investment magnitude, and perspectives on pharmaceutical promotion such as push versus pull).

Chapter six addresses regulation of pharmaceutical marketing activities, studying theories on self-regulation, government regulation, and regulation effectiveness.

Chapter seven presents the conceptual model, built based on the literature review presented from chapters two to six.

Chapter eight makes a brief analysis of health care in Portugal, covering bases on health economics, the pharmaceutical market in Portugal, and the Portuguese pharmaceutical legislative framework overview (years 2000 to 2017), to help understand the specific national framework and to help adjust the methodology to apply in the empirical study.

Chapter nine presents the methodology observed in this thesis, from the literature review, to the empirical study (quantitative and qualitative phases).

Chapter ten covers the quantitative empirical study and chapter eleven addresses the qualitative empirical study.

Chapter 12 covers the discussion, comparing the results from the empirical study against the theory and the conceptual model, while chapter 13 addresses the contributions of our research to the theory, to the industry practice, and to the public policy.

Chapter 14 presents the answer to the research question, chapter 15 explores the conclusions generated by our research and chapter 16 covers the limitations of our work.

Finally, chapter 17 explores our suggestions for future research on the topics of our work, and chapter 18 presents the references.

2. Life sciences industry and life sciences marketing

2.1.Content and logic of the chapter

This chapter addresses the theories on life sciences and life sciences marketing and has the goal of providing a theoretical framework where the pharmaceutical industry and its promotion activities are embedded.

The chapter starts by addressing the reference literature on life sciences industry and its components, the drug research and development process, the distribution channels, and alliances in healthcare. Second, the life sciences marketing is addressed, and its main components are explained. At the end, a reflection on the main issues covered in the reviewed literature is made, as well as their implications on the study of detailing as a promotion instrument in the pharmaceutical industry.

Appendix 1.1 explores the concepts of distribution channels and alliances in healthcare.

2.2.Concepts

Several main concepts are covered in this chapter. The life sciences industry includes three components, which are pharmaceutical industry, biotechnological industry, and therapeutic medical devices industry. Research and development is the process by which the life sciences industry discovers, develops and tests new compounds, which will lead to new medicines launches. Pharmaceutical industry supply chains consist of drug manufacturers, wholesalers, and pharmacies. Alliances represent a mechanism for companies to search for collaborative solutions to common problems, aimed at generating benefits and/or minimizing costs. The life sciences marketing is a novel field in marketing, offering opportunities to study its unique issues and problems. It includes therapy creation, therapy launch, and therapy promotion.

2.3.Life sciences industry

The life sciences industry represents a significant weight in world economy. Latest 2017 global life sciences sector outlook developed by Deloitte (2017) estimates that, by the year 2020, the life sciences weight on the GDP will reach 10,5%, an increase of 0,1 percentage points from the 2015 estimates.

2.3.1. The uniqueness of the life sciences industry

The life sciences industry has several uniqueness features when compared to buyer consumer goods industries. Patients are the payers of the drugs (by their own money or through heatlh insurance), but are not the deciders, since for prescription medicines are chosen by physicians,

who select a drug among a set of alternatives (Gönül et al, 2001), making prescription medicines market part of a captive market (Lexchin, 1997). By other words, the stakeholders who decide the product to prescribe, and to whom most promotional effort is directed, as not the purchasers, as underlined by Caplow & Raymond (1954). They also noted that it is an innovation-based industry where only a few products may have definite success in the market, and where elasticity of demand is low for many products.

This industry is characterized by a peak in drugs' sales trajectories, in terms of both height-of-peak-sales and the time necessary to achieve the peak sales, as noted by Fischer, Leeflang & Verhoef (2010). They explained that this peak is justified by four reasons: first, sales dynamics are mainly driven by first-time prescriptions (physicians do not easily switch to another brand, once the patient is stable taking the first prescribed drug); second, companies employ the majority of their promotion investments in the first two years after the drug launch, which provokes a substantial acceleration on drug sales; third, there is a limit in the prevalence of the specific pathologies, that is, there is a limited number of patients who could benefit from the drug; fourth, new competitors entering the market such as generics and innovative competitors may limit the peak in sales.

2.3.2. Components of the life sciences industry

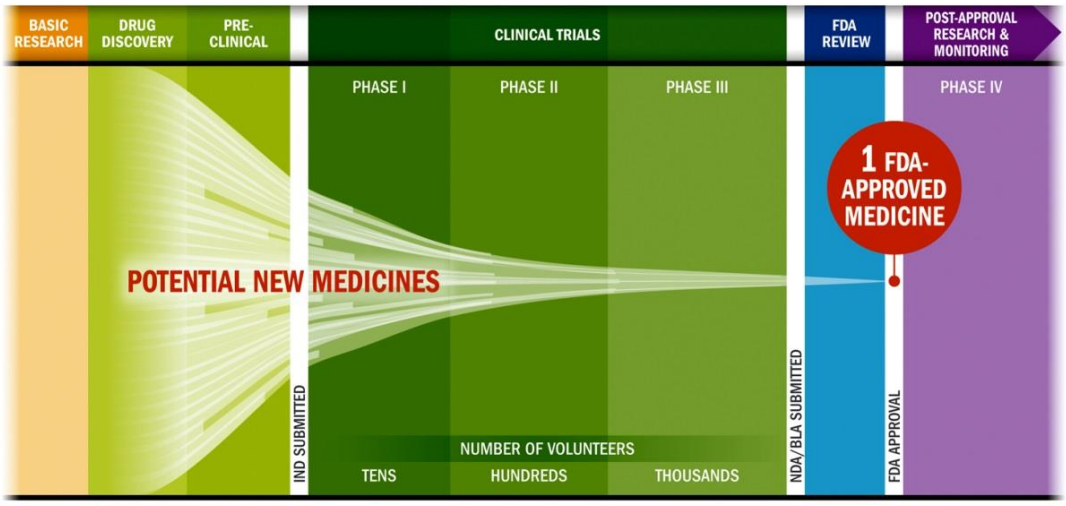
The life sciences industry comprises three components: pharmaceutical industry, biotechnological industry and therapeutic medical devices industry, all of three science and patent based (Stremersch & Van Dyck, 2009). While the pharmaceutical industry develops and markets inorganic compounds (chemically developed drugs such as statins, a class of medicines frequently used to lower blood cholesterol levels, or vasodilators, used in the treatment of hypertension), the biotechnological industry develops and markets organic compounds (such as Humira or Remicade, immunosuppressive agents used in the treatment of autoimmune diseases), and the therapeutic medical devices industry develops and markets instruments, materials, appliances, used for the prevention and treatment of diseases in the human body. Stremersch & Van Dyck (2009) present an example of a situation covering all three components of the life science industry at the same time: in the treatment of breast cancer, pharmaceutical drugs can be used in the chemotherapy process, biologics can be used in targeted therapies to specific patients types, and medical devices can be used the radiotherapy sessions.

Chung, Kim & Park (2017), based on data provided by QuintilesIMS, noted that the global market for prescription drugs is likely to grow from $1.1 trillion in 2016 to $1.5 trillion in 2021, worldwilde.

2.3.3. Drug research & development process

The life sciences industry develops research and development discovering thousands of new compounds. As noted by Sedgwick (2014), the research and development process includes a series of stages, in which drugs are only tested in humans after they have been tested in laboratory. From human testing is then divided in sequential clinical trials called phase I, phase II, phase III and phase IV. According to Sedgwick (2014), «*generally, phase I trials establish safety and tolerability in healthy volunteers; phase II trials determine the drugs' efficacy and adverse effects at different dosages in patients; phase III trials establish the effectiveness and safety of the drug compared with placebo or current standard treatment; and phase IV trials determine general risks and benefits after the drug has been licensed*» (p. 1). Sedgwick (2014) also underlined that the number of participants in each consecutive phase generally increases, and that drugs that do not meet effectiveness and safety strict parameters during the drug development will not be eligible to advance to the next phases.

The Pharmaceutical Research and Manufacturers of America summarized the Biopharmaceutical Research & Development Process (PhRMA (2017), here shown in figure 2.1.



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

Figure 2.1 - The Biopharmaceutical Research & Development Process

Source: PhRMA (2017)

Of the new compounds discovered, only a small percentage of which (between 1 in 5000 to 1 in 10000) will eventually enter the market (Stremersch & Van Dyck, 2009). These newly discovered compounds will experience a preclinical phase where they will be tested to evaluate whether they may potentially provoke serious harm, or cause toxicity, *in vitro* (in a test tube) and *in vivo* (in a body of a living organism), as explained by FDA (2017c). Compounds that successfully meet the preclinical requirements will move to the clinical trials phase, where they will be tested in humans. Considering only the compounds that enter phase 1 clinic development, an average of only one out of ten (10,4%) will move to FDA approval (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014), a situation referred by Ding & Eliashberg (2002) as a pipeline funnel. The estimate of the overall clinical success rate of new compounds that enter phase I and reach marketing approval was confirmed by more recent research conducted by DiMasi, Grabowski & Hansen (2016), suggesting a value of 11,83%.

By diluting the costs on non-FDA approved drugs with the costs of approved drugs, DiMasi, Grabowski & Hansen (2016) estimated a cost of USD$1395 million per new marketing-approved drug, but this estimate rises to USD$2,588 million when considering also the cost of capital invested, or USD$2870 million considering post-approval R&D costs too. Whenever a new drug receives marketing approval, 10 to 12 years on average have passed from the new compound application filling to the end of the clinical development, as highlighted by Stremersch & Van Dyck (2009). They also underlined patents of the new compounds are granted for 20 years before generics can enter the market. A direct implication is that pharmaceutical manufacturers that get their new drugs approved for commercialization will have approximately only 8 to 10 years of market exclusivity.

2.4.Life sciences marketing

The life sciences marketing is, according to Stremersch & Van Dyck (2009) a novel, nascent field in marketing, offering opportunities for scholars to research its specific issues and unique challenging problems, using high-quality available data and that have a significant impact transcending the typical problems generally investigated by marketing researchers.

The life sciences industry key marketing decision areas framework developed by Stremersch & Van Dyck (2009) offers a perspective of the main dimensions scholars and industry professionals may observe in their academic investigation and managerial practices. The first consists of therapy creation, the second consists of therapy launch, and the third consists of therapy promotion (figure 2.2 below), which will be addressed in higher detail in the next points.

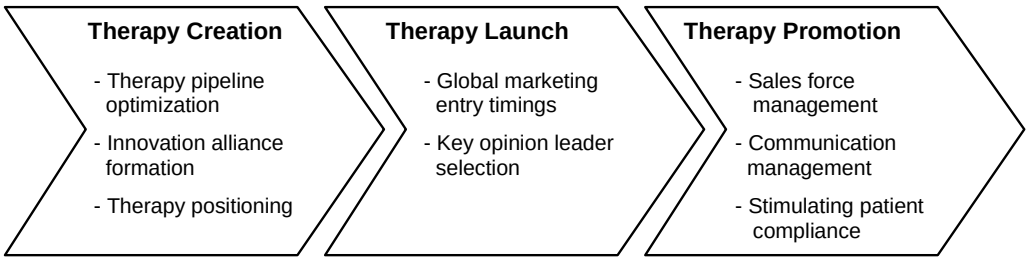


Figure 2.2 - Key Marketing decision areas in the life sciences

Source: Stremersch & Van Dyck (2009)

More recently, Stros & Lee (2015) proposed a more traditional concept view of the pharmaceutical marketing model, shown in figure 2.3. Based in their systematic review of the marketing dimensions in the prescription pharmaceutical industry, they found that «*pharmaceutical promotion as a marketing instrument appears to be considerably more relevant than price, product of place*» (p. 322). They found that promotion policy was substantially more frequent in the literature (97 times mentioned), than price (25), product (16), and place (5).

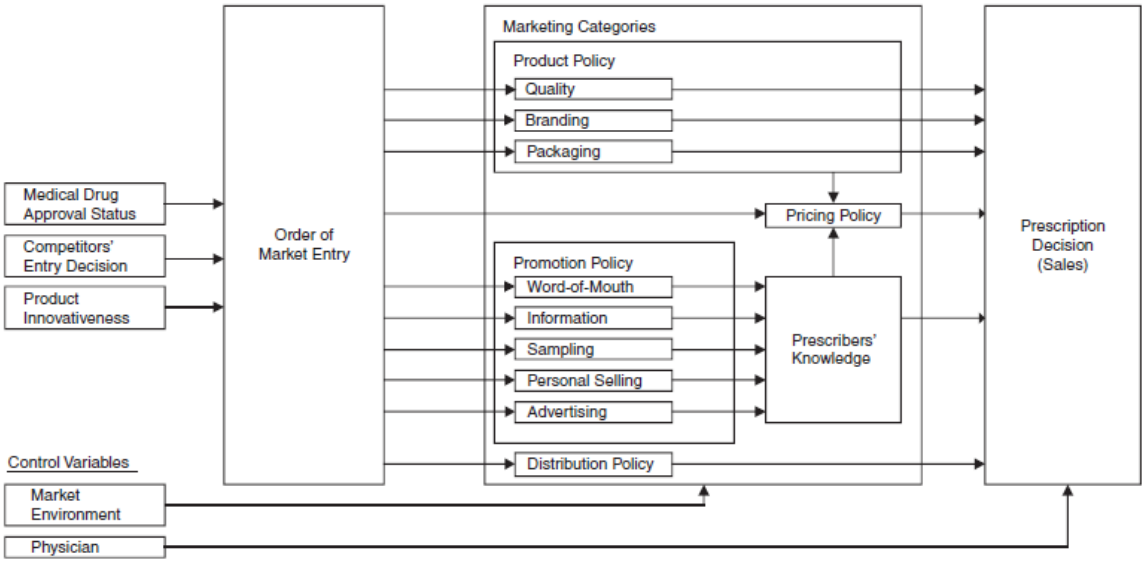


Figure 2.3 - Conceptual pharmaceutical marketing model

Source: Stros & Lee (2015)

We will now detail the life sciences marketing components proposed by Stremersch & Van Dyck (2009).

2.4.1. Therapy creation, therapy launch and therapy promotion

Therapy creation encompasses, as shown in figure 1, therapy pipeline optimization, innovation alliance formation and therapy positioning. Therapy pipeline optimization consists, as noted by Stremersch & Van Dyck (2009), of premarket decisions on portfolio or pipeline optimization, regarding all phases of drug development. Innovation alliance formation is related to decisions concerning alliances during the product development stages. And therapy positioning comprises, as highlighted by Stremersh & Van Dyck (2009), premarket decisions on segmentation and targeting of the product (which they refer to as competitive positioning.

Therapy launch covers global marketing entry timings and key opinion leader selection. As explained by Stremersch & Van Dyck (2009), while the former «*Includes decisions regarding optimal market entry timing, pioneer versus follower advantages, international launch strategy, and new product market potential forecasting»* (p. 9), the later «*includes the structuring of the company's key opinion leader network for maximum effectiveness»* (p. 9).

Therapy promotion comprehends sales force management, communication management, and stimulating patient compliance. Stremersch & Van Dyck (2009) explained these three components. Communication management's perimeter contains the creation of optimal communication strategies (such as medical publications, direct-to-consumer advertising, also known by DTCA (in the US and New Zealand, the only countries allowing DTCA advertising of prescription drugs), and on-line communication with both physician and patient communities. Stimulating patient compliance includes the design of optimized patient compliance programs, which aim, as noted by Stremersch & Van Dyck (2009), patient adherence and welfare to the prescribed treatments, and company profit. Sales force management, the first of the three sub-topics, will be addressed separately in the next topic.

2.4.2. Co-marketing and co-promotion

We will now highlight the concepts of co-promotion and co-marketing.

As noted by Bronder & Pritzl (1992), co-marketing and co-promotion are forms of sales alliances. According to their definitions, while co-marketing is an alliance where a product is distributed and promoted by a company and business partners under a different name, co-promotion involves the promotion of one brand name by a company and selected business partners. In both cases, business partners can be one or more of the company competitors. Carter (2005) noted that co-marketing and co-promotion are forms of joint marketing, and

that while co-marketing involves direct competition by two or more trademarks, co-promotion «*allows two companies to combine their resources and promote the product under one name*» (p. 418). More recently, Liu, Liu & Chintagunta (2017) explained that a co-marketing is an «*agreement in which two companies promote the same chemical but with different brand names*» (p. 3).

These types of alliances may be useful, as noted by Bronder & Pritzl (1992) when addressing the GSK case in the 1980's, when a company may not have the sufficient sales force resources and marketing strength to promote a brand or a drug alone. Bronder & Pritzl (1992) noted that co-marketing may involve some potential for cannibalization, since two or more brands are competing for the same prescribers. Co-marketing may however involve higher costs in terms of marketing and organization, due to the establishment of two or more brands names, and has been losing ground to co-promotion, according to Moss (2001). Carter (2005) also underlined that whereas co-promotion has a greater financial role in the scope of such alliances (mainly when drugs have high sales potential), co-marketing may be more used in local agreements.

Figure 2.4 evidences this increase in the number of deals, here shown as a sum of licensing, co-promotion and co-marketing agreements.

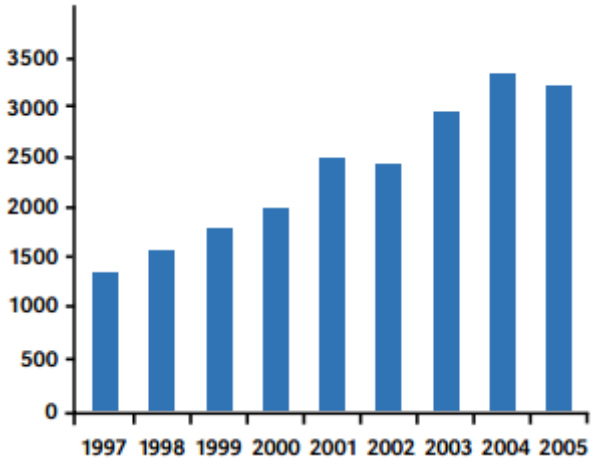


Figure 2.4 – Total annual number of pharmaceutical deals

Source: Carter (2005)

2.5.Chapter synthesis of main findings

In the present chapter a literature review on the components of the life sciences, its brief characterization, and the life sciences marketing was performed. The review allowed identifying the pharmaceutical industry as one of the components of the life sciences industry.

The pharmaceutical industry has several characteristics which contribute to its uniqueness. It is a research and development intensive industry, dependent on a robust pipeline of new compounds discovery, from which only a small percentage will be commercialized, usually representing a cost of more than USD$2500 million per each market-approval new drug.

This chapter also allowed the identification of therapy promotion as one of the pillars of the life sciences marketing. The convergence of pharmaceutical industry by the one hand, and therapy promotion by the other hand, allowed the outlining of the research perimeter to be developed in the empirical part of this thesis (study of detailing, a pharmaceutical marketing promotion tool, in the Portuguese pharmaceutical industry).

3. Sales force management in the pharmaceutical industry

3.1.Content and logic of the chapter

This chapter addresses the theories on sales force management, and its application in the pharmaceutical industry. Its relevance is due to the fact that detailing is an instrument of sales force management (Stremersch & Van Dyck, 2009), which demands an analysis of pharmaceutical industry-related sales force theories.

The chapter starts with the review of base concepts regarding sales force management. Appendix 1.2 addresses the concepts of sales force effectiveness, a central concept in sales force management in the pharmaceutical industry. Upstream in the sales process, this section addresses the physician profiling, segmentation and targeting, moving then to the development of the optimal frequencies for the interactions with clients, in order to define the optimal number of representatives in the sales force team. It also addresses the importance of the sales force structure and design, and the relevance of sales territory alignment. It covers additional processes regarding sales force effectiveness such as recruiting and selection, training, compensation, and supervision and evaluation.

Appendix 1.2 also addresses the theories on customer relationship management (CRM) and sales force automation (SFA) in the pharmaceutical industry. The reasoning for this analysis resides in two main aspects: by the one hand, the importance of CRM as a philosophy in the management of the relationship between pharmaceutical manufacturers and their stakeholders, mainly physicians (the prescribers); by the other hand, SFA theories contribute to a broader understanding of the processes involving the interaction between PSRs and physicians. CRM and SFA concepts in the scope of the pharmaceutical industry will be addressed. It then addresses how manufacturers use information gathered in customer information databases, highlighting the main SFA tools covered in the literature. Closed-loop marketing is covered, highlighting its importance in the pharmaceutical marketing and sales management, since its usage can provide pharmaceutical manufacturers and their PSRs with a broader knowledge of their stakeholders. The sub-chapter then ends with the exploration of the main benefits and main barriers to the implementation of SFA in the scope of the pharmaceutical industry.

Another sub-chapter covers theories on pharmaceutical sales representatives (PSRs), of high relevance due to the fact that they constitute pharmaceutical manufacturers sales force teams, and given that detailing (their job) is the most important promotion instrument in terms of

both investment magnitude and effect on physicians' prescription behavior. Therefore, the study of the main literature on PSRs allows for a broader understanding of the theoretical background of the current thesis. The sub-chapter begins by addressing the main concepts regarding PSRs, namely the definitions present in the literature, and persuasion and reciprocity which are involved in PSRs interactions with physicians. It then addresses PSRs roles (which are both informative and promotional), and explains the different typologies of PSRs (from general PSRs to key account managers). PSRs activities are also explored, with a characterization of the main tasks developed in their daily routine. The sub-chapter then examines the growing difficulty PSRs are facing in their contacts with physicians, due to a significant decline in the access to these stakeholders.

A synthesis of the main findings gathered in the several sub-chapters will then be made.

3.2.Concepts

Kotler & Armstrong (2012) positioned sales force management as part of the personal selling concept, defining the latter as «*the interpersonal arm of the promotion mix. A company's sales force creates and communicates customer value through personal interactions with customers*» (p. 464). They continued by noting that «*personal selling involves interpersonal interactions between salespeople and individual customers—whether face-to-face, by telephone, via e-mail, through video or Web conferences, or by other means*» (p. 465), also underlining the two main roles of the personal selling: linking the company with its customers, and coordinating marketing and sales.

Following Stremersch & Van Dyck (2009) framework, sales force management encompasses decisions on optimal sizing (number of pharmaceutical sales representatives) and targeting (selection of the right physicians to impact with detailing activities) of the sales force, decisions that optimize sales call quality (defining the optimal drug attributes to be discussed with the physicians during a sales call), and the optimization of the use of drug samples, including sales response models such as the impact of detailing on prescription behavior.

Figure 3.1, developed using Stremersch & Van Dyck framework, evidences detailing as one of the instruments of sales force management.

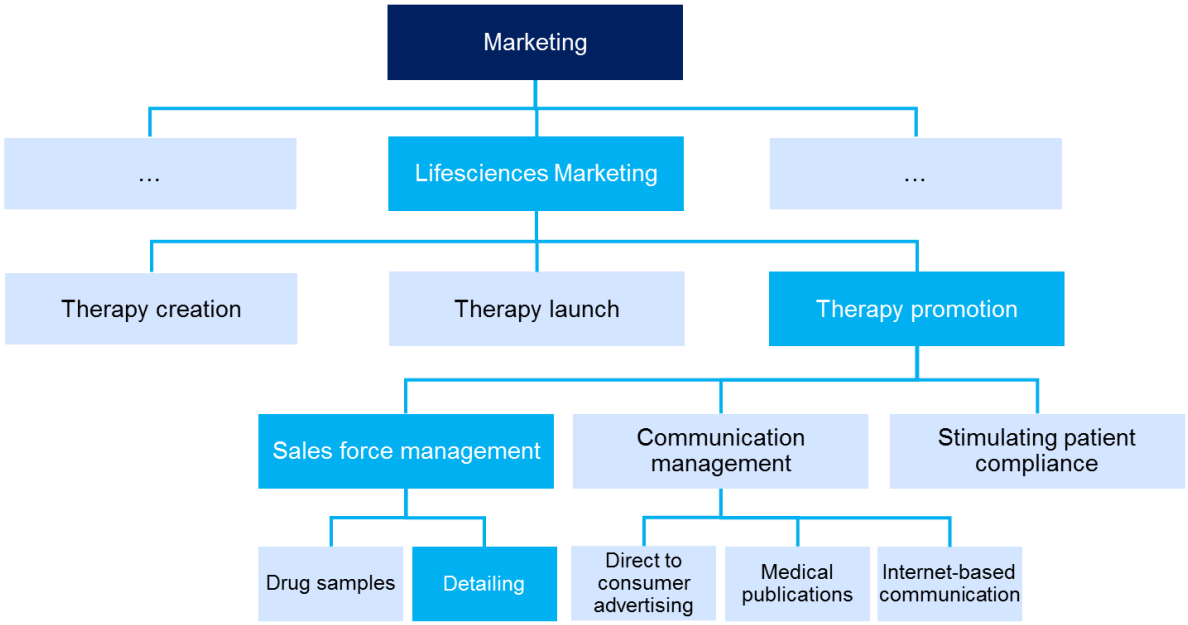


Figure 3.1 - Marketing of the Life Sciences

Source: adapted from Stremersch & Van Dyck (2009)

Kotler & Armstrong (2012) defined sales force management as «*analyzing, planning, implementing, and controlling sales force activities. It includes designing sales force strategy and structure and recruiting, selecting, training, compensating, supervising, and evaluating the firm's salespeople*» (p. 468). According to Drexl & Haase (1999), «*sales force deployment involves the concurrent resolution of four interrelated subproblems: sizing the sales force, salesman location, sales territory alignment, and sales resource allocation*» (p. 1).

Another concept in the scope of sales force management is sales force effectiveness (SFE, appendix 1.2). As noted by Zoltners, Sinha & Lorimer (2008), sales force effectiveness involves a series of drivers including a set of basic decisions, processes, systems, and programs that impact the sales structure, salespeople, and activities. Sales force effectiveness addresses sales analytics and profiling, segmentation, targeting, call planning, sales force sizing and structure, territory alignment, salesforce recruiting, evaluation, compensation, and supervision and evaluation, concepts that are individually covered in the SFE sub-chapter (appendix 1.2).

Customer relationship management and sales force automation concepts are also covered in appendix 1.2. Pharmaceutical companies have the need of handling substantial amounts of data from their clients (physicians and other stakeholders), which needs to be gathered, analyzed, classified and disseminated, in order to properly feed and support the sales force

effectiveness processes. In this scope, a customer relationship management (CRM) vision is important, in order to enhance customer relationships, through sales force automation (SFA) technological tools. CRM consists of processes and technologies that enhance customer relationships, and SFA handles only with technological tools. Consequently, CRM is a more comprehensive concept than SFA. A full sub-chapter addresses CRM and SFA theories in more detail (appendix 1.2).

Pharmaceutical sales representatives (PSRs), also called reps, or detail men (Caplow & Raymond, 1954; Williams & Hensel, 1991), are trained salespersons employed by pharmaceutical companies. They visit physicians providing them information, education, gifts, drug samples, and free meals, with the goal of both provide scientific support and promote medicines. PSRs try to persuade physicians to prescribe the promoted medicines.

3.3.Pharmaceutical sales representatives

Pharmaceutical sales representatives, also called reps, or (formerly) detail men (Caplow & Raymond, 1954), are trained salespersons employed by pharmaceutical companies. As suggested by Alkhateeb et al (2011), PSRs «*are employed to provide education specific information and material to physician offices, hospitals, pharmacies, and other healthcare providers*» (p. 224), in an attempt to increase prescription volume by influencing prescribers.

The regular contact PSRs have with physicians, presenting scientific information, but also providing free office and sometimes personal gifts, as well as free meals, may be discussed under Gass & Seiter (2016) complete model of persuasion, in the sense that detailing can be a situation of face-to-face persuasion. The relation between PSRs and physicians can also be analyzed using Cialdini (1993) principles of persuasion.

Roughead, Harvey & Gilbert (1998), when studying general practitioners audiotapes of encounters between PSRs and physicians (detailing), found that the reciprocity principle was the most frequent principle observed in the audiotapes, including «*sample supply, gifts, printed material, patient information leaflets and invitations*» (p. 308). By the virtue of the reciprocity rule, physicians may feel obligated to reciprocate PSR regular assistance and free meals by increasing the likelihood of prescribing the medicines brands they promote. Roughead, Harvey & Gilbert (1998) presented an example of a reciprocation act: «*Doctor: I've used 'Your Brand' on a couple of occasions when I've had samples of it and had a good response to it…*» (p. 308). Katz, Caplan and Merz (2010) also noted that physicians may feel

bound to reciprocate PSRs, due to their support. Other researchers have addressed Cialdini's principle of reciprocity in the scope of detailing. Sah & Fugh-Berman (2013) synthetized pharmaceutical industry influence tools on prescribers in three levels: national (through industry grants to medical organizations and public-private partnerships), institutional (educational grants, continuous medical education, travel expenses) and individual (fees for research, consulting, speaking, gifts of meals, medical equipment and books).

Other Cialdini (1993) principles of persuasion may apply to the interactions between PSRs and physicians. Roughead, Harvey & Gilbert (1998) found evidences of the principles of authority (by quoting professors, medical specialists, specialist groups and specialist hospitals), social validation (using "other doctors" reference as a peer group), and commitment/consistency (involving a direct request for prescriptions, or a series of questions or statements that conducted physicians to express an agreement to prescribe the drug), frequently used by the PSRs in order to influence physicians' prescription behavior.

3.3.1. Roles

PSRs provide a series of roles in the pharmaceutical industry, in their interactions with physicians. One of which is to provide physicians with important information about a drug's composition, its therapeutic value and side effects, and adequate dosage, as noted by Parsons & Abeele (1981). Wright & Lundstrom (2004) referred that PSRs responsibility is to provide credible product information to physicians, in a more and more controlled environment such as reduced access to physicians.

PSRs also have a role in pharmaceutical marketing, as important marketing and sales instruments, according to Scharitzer & Kollarits (2000). PSRs role is also to «*assess physicians' personalities, practice styles, and preferences, and to relay this information back to the company*», since «*personal information may be more important than prescribing preferences*» (Fugh-Berman & Ahari, 2007, p. 621). Caplow & Raymond (1954) explained that PSRs primary role is to «*describe products and to maintain good public relations so that the physician will be favorably disposed to the company and its products when he comes to the writing of prescriptions*» (p. 18).

3.3.2. Typologies

Alkhateeb et al (2011) distinguished three types of PSRs: general PSRs, specialized PSRs, and medical liaisons (or medical science liaisons, or MSLs).

General pharmaceutical sales representatives

General PSRs visit physicians usually at their offices and are typically seen visiting prescribers and pharmacists. As noted by Alkhateeb et al (2011), general PSRs usually have a high knowledge not only about the drugs they promote, but also about competitor drugs, and hand physicians with merchandising materials such as pens and pads, aimed at increasing physician awareness of the promoted products.

Specialized pharmaceutical sales representatives

Specialized PSRs generally work in hospital settings. As noted by Alkhateeb et al (2011), hospitals present a very specific situation to pharmaceutical companies, since physicians usually may not have the ability of prescribing all the drugs available, due to the existence of hospital formularies, regulated by a pharmacy and therapeutics (P&T) committee, which includes «*physicians, pharmacists, nurses, and other appointed healthcare professionals*» (p. 224). This main difference to the ambulatory market demands a specific type of PSR, more focused on negotiation in order to get the promoted products available in the hospital formulary. Alkhateeb et al (2011) also noted that these specialized PSRs may be involved in group purchasing organizations (GPO), created to take advantage of volume discount contracts.

Medical science liaisons

Medical liaisons are a type of PSR with a clinical background. As explained by Alkhateeb et al (2011), medical liaisons can promote products alongside or as opposed to general PSRs. They also highlighted that medical liaisons usually have scientific or healthcare degree such as a PhD, a MD, or a PharmD, and that they receive sales training too. According to Moss & Black (2013) survey of academic and practicing KOLs, MSLs' role is also important in providing KOL with education, information, professional network, and engaging in intellectual conversations. Baker (2010) suggested that medical science liaisons may be considered as "glorified sales representatives", and underlined the main differences between PSRs and MSLs: while both must be prepared to explain the drugs or devices mechanism of action, the MSL goes beyond this, being able to «*discuss in the background science, related research, and pharmacokinetics of the product*» (p. 395). Nair, Manchanda & Bhatia (2010) characterized MSLs as «*special teams consisting of higher-caliber detailers*» (p. 884).

MSLs roles can include, as noted by Jacob (2018), preparation and review of drug literature, guaranteeing its compliance with regulation, training of the PSRs team on scientific and medical aspects of the promoted drugs, and keeping good relations with KOLs in the industry.

Key account managers

The increased pressure on medicines prices, the generics competition, and eroding margins of branded medicines led pharmaceutical companies, as noted by Alt, Österle, Puschmann, Barak & Huber (2003), to adopt a new type of PSR – Key account managers (KAMs). KAM role has expanded from simple promotion activities, to include, as highlighted by Padhy & Patnaik (2008), «*local account strategy, team selling, focused expertise, training, coaching and mentoring activities*» (p. 7). Key account management is a sales channel, and typically takes care of big customers including hospitals, wholesalers, and pharmacies (Puschmann & Alt, 2001). As underlined by Padhy & Patnaik (2008), the key account management approach allow sales and medical representatives to build strong relationships not only with key prescribers, but also with prescribers' influencers, by analyzing and understanding their professional needs and factors underlying their prescription decisions.

3.3.3. Activities

PSRs typically have a panel of 200 physicians, of which 120 should be visited in four to six weeks cycles (Sfetcu, 2014). They do not sell drugs directly to buyers (patients), targeting instead physicians, trying to influence them to increase the promoted drugs sales (Fugh-Berman & Ahari, 2007). Salmasi et al (2016) noted that PSRs job is to introduce and market their companies' products, using, in the interaction with physicians, several promotion instruments such as free drug samples, gifts, free meals and sponsorships.

Pharmaceutical sales representatives can make between five and ten visits per day (Datta & Dave, 2016). Parsons & Abeele (1981), and Yi, Anandalingam & Sorrell (2003) suggest that PSRs visit, on average, seven physicians per day. The number of visits per day can however vary depending on the medical specialties visited, geographic dispersion of the doctors to visit, and other factors. For instance, oncology PSRs typically are assigned five visits per day, but only can perform an average of less than three (ZS Associates, 2013).

In each visit, the reps can present more than one detail (one detail is one product mention), so a single sales call can produce several detail contacts with phsycians (Berndt, Danzon & Kruse, 2007). Parsons & Abeele (1981) suggested that the number of details per visit is three (that is, three products mentions during one call).

3.3.4. Declining access to physicians

According to a ZS Access Monitor report (ZS, 2016a), based on call activity of more than 40,000 sales representatives on more than 400.000 prescribers, 44% of physicians are considered accessible in 2016. This number compares to 47% in 2015, 51% in 2014, 55% in 2013, 65% in 2012, and nearly 80% in 2008, meaning that pharmaceutical reps may be facing some challenges regarding access to some physicians. The same report states that «*38% of reps were 'access-restricted' (…) and 18% were severely 'access-restricted'"* (p. 1).

Figure 3.2 evidences the higher difficulty PSRs are experiencing in reaching physicians, showing an almost linear tendency.

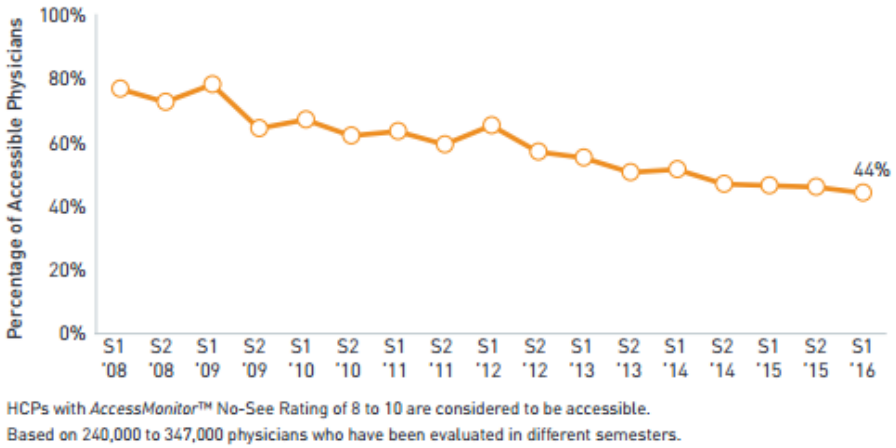


Figure 3.2 – PSRs declining access to physicians – Years 2008 to 2016

Source: ZS (2016a). Access MonitorTM and Affinity MonitorTM 2016 Executive Summary

Analysing the trend of the curve, it may be likely that in the near future the accessibility to physicians may become even more difficult. This observation is aligned with the ascension of alternative communication channels and promotion tools, as will be covered later in this thesis.

3.3.5. Sub-chapter synthesis of main findings

Pharmaceutical sales representatives are salespersons hired by pharmaceutical companies to provide health care practitioners (mainly physicians) to provide information, education, materials, but also gifts and free meals. They are also known as reps or detail men and have the roles of delivering scientific content to prescribers (on drug composition, therapeutic value, side effects and dosage), providing credible product information, and of being a

marketing and sales instrument, maintaining good relations with physicians. Research has demonstrated the reciprocity rule in the interactions PSRs keep with physicians. There are four types of PSRs: general PSRs (which typically visit physicians and pharmacists, having a high knowledge of their company drugs and their competitors'), specialized PSRs (which typically work in hospital settings, and may be involved in group purchasing), medical science liaisons (which have a clinical background, and promote products alongside or as opposed to general PSRs), and key account managers (whose roles include local account strategy, team selling, focused expertise, training, coaching and mentoring activities, managing big customers or accounts).

A PSRs' normal panel reaches around 200 physicians, 60 per cent of which is visited monthly or every one and a half months. PSR normally visit five to ten physicians per day, but this number depends on a series of factors (medical specialties, geographic dispersion, and other). In each visit, PSRs present approximately three products (three different product mentions, or three details). The detailing activity has however been suffering some difficulties, mainly due to a growing decline in the access to physicians.

Table 3.1, developed after the literature review on pharmaceutical sales representatives and sales force management (thesis main document and appendix 1.2), explores a general PSRs typical characterization.

Table 3.1 – General PSR characterization

	Scope		Brief description	Theoretical grounding (non-exhaustive)
Pharmaceutical sales representatives (PSRs)	General characterization	Roles	Provide education and material to physician offices; credible product information about a drug's composition, therapeutic value, side effects, dosage	(Parsons & Abeele, 1981; Wright & Lundstrom, 2004; Alkhateeb et al, 2011)
			Act as marketing and sales instrument in promoting medicines, to influence physicians increase prescriptions; maintain good public relations to increase physician willigness to prescribe the promoted medicines	(Caplow & Raymond, 1954; Scharitzer & Kollarits, 2000; Fugh-Berman & Ahari, 2007)
			Collect information about physicians and relay it to the company	(Fugh-Berman & Ahari, 2007)
		Typologies	General PSRs, specialized PSRs, medical science liaisons (MSLs), key account managers (KAMs)	(Puschmann & Alt, 2001; Alt, Österle, Puschmann, Barak & Huber, 2003; Alkhateeb et al, 2011)
		Desired profile	Friendliness and trustiness	(Andaleeb & Tallman, 1996)
			Warm, easy going, and cooperative; dominant and shrewd	(Sager & Ferris, 1986)
			Agreeableness and openness to experience	(Thoresen, Bradley, Bliese & Thoresen, 2004)
			Adequate non-verbal skills	(Peterson, Cannito & Brown, 1995; Leigh & Summers, 2002)
			Innovative (creative) personality type; higher emotional commitment	(Fraenkel, Haftor & Pashkevich, 2016)
		Qualifications	Typical: college (bachelor or associate) degree	(Alkhateeb et al, 2011)
			Business, marketing, chemistry, biochemistry, and biophysics (and some cases of English, public speaking, finance, economics and law)	(Alkhateeb et al, 2011)
		Training	Hard skills: medical terminology, pharmacology, sales, marketing, diseases and pharmacology, and general knowledge of the human body	(Alkhateeb et al, 2011)
			Soft skills: non-verbal skills	(Peterson, Cannito & Brown, 1995; Leigh & Summers, 2002)
		Compensation	Fixed + variable component (quota-based bonus)	(Mantrala, Sinha & Zoltners, 1994; Goldberg & Davenport, 2005; Alkhateeb et al, 2011; Fraenkel, Haftor & Pashkevich, 2016; Santiago, 2017)
			Typical situation: fixed component weights 85%, variable weights 15%	(Mantrala, Sinha & Zoltners, 1994)
			Σ (Base salary + bonus) = average $81,700 per year	(Goldberg & Davenport, 2005)
			Company car, medical and tuition reimbursement, and retirement plans	(Santiago, 2017)
		Supervision and evaluation	Direct report to regional sales chief or district sales manager	(Mantrala et al, 2010)
			60% of the bonus based on the individual sales performance in territories (against sales goals) + 40% based on management assessment (qualitative)	(Mantrala, Sinha & Zoltners, 1994)
			Bonus applicable after a minimum threshold (ex: 90%), and capped if performance is higher than a maximum threshold (ex: 110%)	(Mantrala, Sinha & Zoltners, 1994)
	Activity	Client panel	Typical panel: 200 physicians, of which 120 should be visited in four to six weeks cycles	(Sfetcu, 2014)
		Detailing	Typical detailing activity: between five and ten calls (visits) per day, with an average of 7 visits per day	(Parsons & Abeele, 1981; Yi, Anandalingam & Sorrell, 2003; Datta & Dave, 2016)
			Average number of details (product mentions) per call (visit): three	(Parsons & Abeele, 1981)
			Typical call duration declining (1997 = 8 minutes; 2001 = 4 minutes; 2007 = up to five minutes)	(Yi, Anandalingam & Sorrell, 2003; Steinman, Harper, Chren, Landefeld & Bero, 2007)
		Non-selling	Pre-call planning (call preparation)	(Mehta, 2004; Ahmad, 2013)
			Sales call reports (insert data with SFA tools)	(Widmier, Jackson & McCabe, 2002)
			Post-call analysis (analyze the call and prepare the follow-up call	(Morgan & Inks, 2001; Mehta, 2004)
			Expense reports	(Morgan & Inks, 2001; Widmier, Jackson & McCabe, 2002)

Source: own elaboration

3.4.Chapter synthesis of main findings

In the present chapter a literature review on sales force management and its application to the pharmaceutical industry was performed. Several relevant evidences were gathered from this

chapter. The first was the evidence that detailing, a form of face-to-face personal selling (Fischer & Albers, 2010), is a promotion tool pharmaceutical manufacturers use to interact with physicians through salespersons known as pharmaceutical sales representatives or PSRs (Mizik & Jacobson, 2004), and therefore is an instrument of sales force management (Stremersch & Van Dyck, 2009). The second is the evidence that sales force management in the pharmaceutical industry is a complex process.

Pharmaceutical sales representatives are salespersons hired by pharmaceutical companies to promote medicines, and to provide physicians information, education, materials, promotional gifts, and free meals. They represent the promotion vehicles of detailing activities pharmaceutical manufacturers develop with physicians, and therefore are critical players from the companies' side. Depending on the pharmaceutical company, degree of specialization needed, type of client (individual or institutional), companies may use more than type of PSR. These types include general PSRs, specialized PSRs, MSLs and KAMs. PSRs' main task is to visit physicians, an activity called detailing, where PSRs present information about several products (each product mentioned represents one detail) to an average panel of 200 physicians. PSRs usually make an average of seven calls per day (in an interval between five to 10 calls per day), yet have been growingly experiencing a decline in the access to physicians, and a decline in the average duration of each sales call.

This chapter therefore sets the pavement for the further analysis of theories on physicians (the main targets of pharmaceutical marketing activities), medical prescription (the medical act that is almost exclusive of physicians, since they are granted the statutory authority to prescribe prescription drugs), and pharmaceutical promotion (with a special focus on detailing).

4. Physicians and medical prescription

4.1.Content and logic of the chapter

This chapter addresses the theories on physicians and on medical prescription. The relevance of these theories is founded in two main pillars: first, physicians are the pharmaceutical industry stakeholders with statutory authority to prescribe prescription drugs, which makes them the main targets of pharmaceutical marketing; second, prescription is a medical act with a very complex nature, influenced by several factors. The study of these two issues will help generate important understanding to subsequent chapters in the literature review, regarding pharmaceutical marketing promotion tools.

The chapter starts by addressing theories on physicians and their roles in the pharmaceutical industry including prescription, communication and participation in health care management. The chapter then addresses medical prescription, explains the difference between prescription and non-prescription drugs, and explores the factors influencing physicians' prescription behavior, which can be marketing and non-marketing related. Following, it will address the prescription decision making process, ending with a synthesis of the main findings gathered in this chapter.

4.2.Concepts

Physicians have the statutory authority to prescribe prescription drugs. This privilege is only shared with some non-physician professional categories in some countries such as the US and Australia, where some nurses and physician assistants may prescribe some prescription drugs too (Ladd & Hoyt, 2016). Given this authority, physicians are the main deciders in the buying decision process regarding prescription drugs (Gönül et al, 2001), and due to their ability to write drug prescriptions, physicians control more than four fifths of health care expenditures, by prescribing or recommending products to their patients (Weeks, Wallace & Kimberly, 2001).

According to Belknap et al (2008), a prescription «*is a health-care program implemented by a physician or other qualified practitioner in the form of instructions that govern the plan of care for an individual patient*» (p. 385). A simpler, more direct definition of medical prescription – which appears to be more common among the practitioners in the pharmaceutical industry – is proposed by the Oxford dictionary: «*an instruction written by a medical practitioner that authorizes a patient to be issued with a medicine or treatment*»

(Oxford Dictionaries, 2017a). The term "prescription" is usually abbreviated by the Rx symbol, shown in figure 4.1 below.

Figure 4.1 – Medical prescription symbol

While in some countries, such as the US and Australia, some nurses and physician assistants have the statutory authority to prescribe drugs (Ladd & Hoyt, 2016), the authority to write a prescription for prescription drugs is generally a privilege attributed to physicians. Gönül et al (2001) noted that physicians have the privilege of prescribing, as the main deciders in the buying decision process regarding prescription drugs. Weeks, Wallace & Kimberly (2001) indicated that, due to their ability to write drug prescriptions, physicians control more than four fifths of health care expenditures, by prescribing or recommending products to their patients.

4.3.Physicians

As noted by Williams & Hensel (1991), physicians have long been considered as gatekeepers in the process of purchasing pharmaceutical products, since consumers cannot purchase ethical medicines (those who need a prescription) without a prescription written by a physician.

4.3.1. Roles in the pharmaceutical industry

Communication with patients can be seen as the main ingredient in medical care, as one of the most important roles of physicians, as addressed by Ong, De Haes, Hoos & Lammes (1995) in their review of doctor-patient communication. They underlined that there are three purposes of communication, which are the creation of a good inter-personal relationship between the physician and the doctor, the exchange of information, and the physician decisions on treatments. As noted by Classen & Kilbridge (2002), physicians' participation is the basis of any health care delivery organization's efforts to improve the safety of care provided to patients. In addition to decisions in the scope of physician-patient relation, physicians' role can include other areas of health care. Leatt (1994) addressed physicians' increasing responsibilities for the «*management of human and financial resources in health care, particularly in hospitals*» (p. 171), and the fact that physicians also have, besides clinical,

teaching, research and management roles, underlining their importance in the shaping of the future of health care. Leatt (1994) also addressed processes where physicians will increasingly participate, including policy and political processes, client or patient-focused approaches, decisions based on data, program definition and management, strategic alliance building, systems-level quality improvement, and human resources management.

Physicians are the main targets of pharmaceutical marketing. The relation developed with the pharmaceutical industry starts many times at the academy and continues during full professional life. As the main prescribers in a multi-billion-dollar market, it is important to study their perception about their relationship with the pharmaceutical industry. As noted by Gönül et al (2001), prescribers are the deciders in the buying decision process, not the patients. Patients are the users and payers (out-of-pocket or through health insurance). This difference from the drug choice process and the traditional decision buying process seen on consumer goods highlights the importance of physicians in the pharmaceutical marketing. The pharmaceutical industry understands this specificity, using multiple promotion instruments, including detailing. Wazana (2000) noted that most physicians receive pharmaceutical sales representatives about four times a month.

4.3.2. Generalists and specialists

According to Oxford Dictionaries (2017b), a physician is «*a person qualified to practice medicine, especially one who specializes in diagnosis and medical treatment as distinct from surgery*». Generally, physicians can be classified as generalists (or general practitioners, or GPs), or specialists, having different but complementary knowledge and skills (Marshall, 1998). The World Health Organization (2008), in its Health Workers Classification, defined both generalists and specialists, which include the responsibility perimeter and disease specificity of each doctor category: «*Generalist medical doctors (including family and primary care doctors) diagnose, treat and prevent illness, disease, injury, and other physical and mental impairments and maintain general health in humans through application of the principles and procedures of modern medicine. They plan, supervise and evaluate the implementation of care and treatment plans by other health care providers. They do not limit their practice to certain disease categories or methods of treatment, and may assume responsibility for the provision of continuing and comprehensive medical care to individuals, families and communities*», and «*specialist medical doctors diagnose, treat and prevent illness, disease, injury and other physical and mental impairments using specialized testing, diagnostic, medical, surgical, physical and psychiatric techniques, through application of the*

principles and procedures of modern medicine. They plan, supervise and evaluate the implementation of care and treatment plans by other health care providers. They specialize in certain disease categories, types of patient or methods of treatment, and may conduct medical education and research activities in their chosen areas of specialization». Traditionally, generalists were educated by specialists in postgraduate courses, although currently specialists are considered more as consultants to GPs, as underlined by Berendsen et al (2009).

According to Bowling & Redfern (2000), a substantial amount of work is performed by generalists, prior to the eventual decision of referring patients to hospitals, asking for the opinion of a specialist. Generalists typically refer patients to specialists such as orthopedic surgeons and gynecologists, as addressed by Piterman & Koritsas (2005), the main reasons being diagnosis or investigation, treatment and reassurance (reassurance for the generalists themselves, as well as reassurance for the patient). Piterman & Koritsas (2005) noted that generalists will choose specialists based on the specialists' skills and generalists' previous experience with the specialist, quality of communication, specialists' office location, and patient preference on specific specialists. They also explained that the referral process is usually made by telephone or by letter, which specialists expect to contain information about the patient problem and patient history.

4.3.3. Prone to detailing profile

Alkhateeb, Khanfar, & Clauson (2009) studied the characteristics of physicians who frequently see PSRs. Using a survey answered by 671 doctors and multiple regressions to analyze the impact of doctor and practice setting characteristics on frequency of monthly visits by PSRs, they found that primary care doctors are more likely to see PSRs, as well as high volume prescribers. They also found that doctors working at small and urban practices are more likely to see PSRs. Other conclusions that emerged from Alkhateeb, Khanfar, & Clauson (2009) research were that doctors who practice in organizations that do not pose restrictive policies for pharmaceutical detailing are more likely to receive PSRs visits, as well as doctors who do not have academic affiliations.

4.3.4. Heavy prescriber profile

Physicians' prescription behavior in terms of number of prescriptions may be related to certain physician characteristics. Gönül & Carter (2012), when analyzing how physicians respond to marketing promotion tools, studied the heavy prescribers' profile for established and new drugs. They found that heavy prescribers for established drugs are typically specialists, usually with more experience, receiving more PSRs (subject to a higher call

pressure from the pharmaceutical industry), having a greater ratio of patients in HMOs, and a higher number of prescriptions from all therapeutic classes. This type of prescribers also receive a higher number of patients in their practices, tend to receive more drug samples from PSRs, receive more PSRs at their offices, and typically allow for longer than average visits duration by PSRs. They also found that heavy prescribers for new drugs typically have more affiliations with health maintenance organizations (HMOs), and tend to work at solo practice (that is, not in groups or with partners),

4.4.Medical prescription

4.4.1. Prescription vs non-prescription drugs

In terms of prescription, the United States Food and Drug Administration (FDA) classifies drugs as prescription and non-prescription (or over-the-counter, or OTC), as underlined by Gabay (2013). Gabay (2013) also noted that a prescription medication, according to the FDA, must be «*dispensed under a valid prescription if, because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug»* (p. 198).

Non-prescription, or OTC drugs are, on the opposite, drugs than can be purchase directly in a retail pharmacy, where the term originated, without a prescription (Cooper, 2013). The FDA describes an OTC drug as a «*medicine that you can buy without a prescription. They are safe and effective when you follow the directions on the label and as directed by your health care professional»* (FDA, 2017a).

The FDA (2017b) summarizes the concepts of prescription and non-prescription drugs in a straightforward and clear way: while prescription drugs are prescribed by a doctor, bought at a pharmacy, prescribed for and intended to be used by one person, and regulated by FDA through the New Drug Application (NDA) process, non-prescription (or OTC) drugs are drugs that do not require a doctor's prescription, bought off-the-shelf in stores, and regulated by FDA through OTC Drug monographs.

4.4.2. Computerized prescription and clinical decision support systems

In the last two decades, the development of computers and software has allowed new possibilities to aid the prescription process. Computer-based physician order entry (CPOE) systems referred by Berner & La Lande (2016), also known by electronic prescription, have been increasingly used by physicians. As noted by research conducted by Bates et al (1998),

the introduction of CPOE systems reduced the rate of non-intercepted serious medication errors significantly (by more than 50%), and also substantially reduced adverse drug events (though this reduction was more modest). Teich, Merchia, Schmiz, Kuperman, Spurr & Bates (2000) analyzed the impact of the usage of CPOE in prescribing practices, by studying a time series of prescriptions and comparing it to non-CPOE prescribing history. They found that, by providing support and suggestions in the CPOE system, the proportion of cases where the prescribed dose exceeded the maximum recommended dose were significantly reduced, and that a higher proportion of prescriptions observed the suggested options provided by the system, contributing to better physician prescription practices.

Physicians may benefit from clinical diagnostic decision support systems (DDSS), which consists of «*a computer-based algorithm that assists a clinician with one or more component steps of the diagnostic process*» (Miller & Geissbuhler, 1999, p. 101). This concept is also known by clinical decision support systems (CDSS), which according to Berner & La Lande (2016) consist of «*computer systems designed to impact clinician decision making about individual patients at the point in time that these decisions are made*» (p. 3). These systems are designed to assist on medical prescription and minimize prescription errors, providing support before, during and after the prescription decision has been made by the physician. As referred by Berner & La Lande (2016), these systems may be knowledge based (that rely on a base of rules such as IF-THEN, of for instance drug-food interactions, and probabilistic associations of signs and symptoms with diagnoses), or non-knowledge based (systems using machine learning from past experiences and pattern recognition). As noted by Berner & La Lande (2016), the later include artificial neural networks, which emulate human thinking in a non-linear form, and genetic algorithms, where sets of solutions are tested until a final, optimal solution is reached. According to Berner & La Lande (2016), CDSS «*have been shown to improve both patient outcomes, as well as the cost of care*» (p. 8), by minimizing prescription errors (alerting physicians to drug interactions) and improving physician diagnoses (using reminders and alerts).

Wolfstadt, Gurwitz, Field, Lee, Kalkar, Wu & Rochon (2008), in their systematic review on the effect of computerized physician order entry with clinical decision support, had already evidenced that in half of the eligible studies selected for analysis there was a significant reduction in the number of adverse drug events.

4.4.3. Factors influencing prescription behavior

Campo, Staebel, Gijsbrechts & Van Waterschoot (2006) concluded that prescription decision making may be a very sensitive and complex process, underlining that «*for pharmaceutical companies and their sales representatives, this would imply that persuading prescribers to switch to another–existing or newly introduced–drug is not an easy task*» (p. 97). Spiller & Wymer (2001) had already suggested that «*physician prescription choice behavior is complex*» (p. 102).

Several researchers have studied the factors impacting physicians' prescribing decisions of prescription drugs. Campo et al (2006) developed qualitative research aimed at understanding the mechanics driving drug prescription behavior, how physicians make the decision to prescribe. They developed in-depth interviews with physicians, using projective techniques (asking them to comment on prescription decision alleged made by a fellow physician). One of their conclusions is that prescription decisions seem to be hybrid in nature, incorporating a series of decision rules, also suggesting that physicians tend to consider a limited number of drug possibilities, and even a smaller number of drugs they usually prescribe. Spiller & Wymer (2001) noted that profession (such as journals, and other physicians, but also the government with for instance drug prescribing restriction policies), pharmaceutical industry promotion activities (including detailing, samples and journal ads), personal experience of the physician, consumers, and affordability (such as cost of drug, insurance possession, and reimbursement) also impact physicians prescription decisions. Figure 4.2 summarizes these factors suggested by Spiller & Wymer (2001).

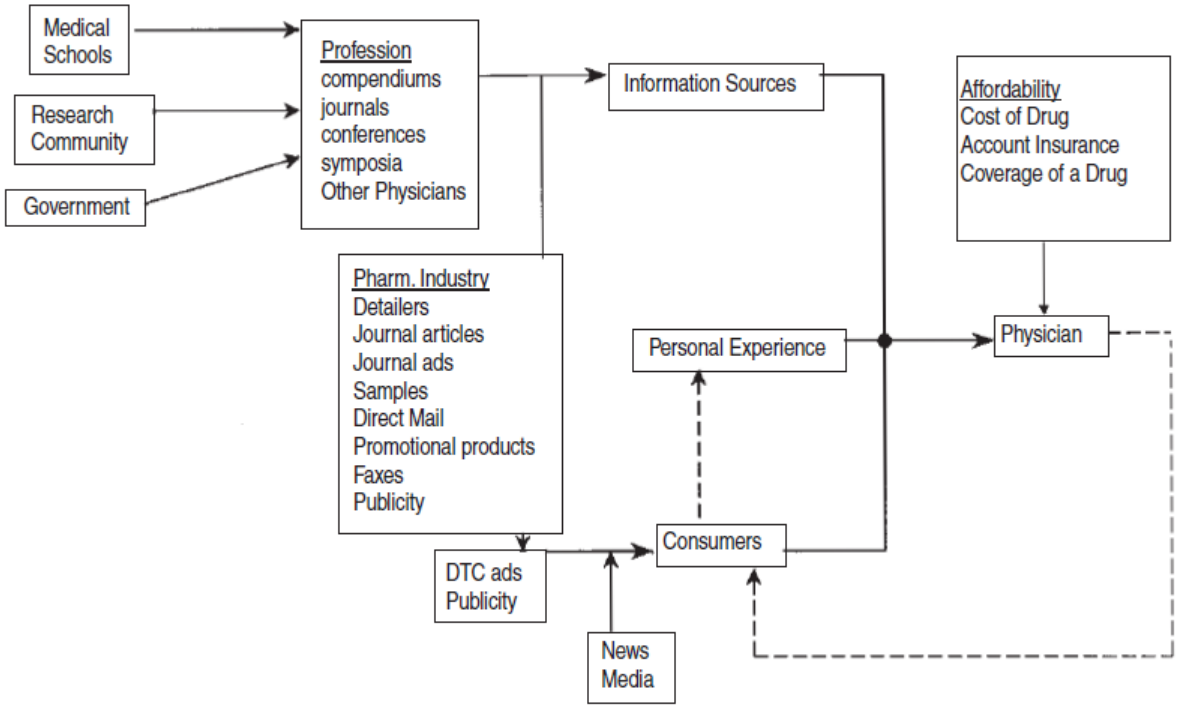


Figure 4.2 – Influences on physicians' prescribing behavior

Source: Spiller & Wymer (2001)

Stros & Lee (2015). In their conceptual pharmaceutical marketing model, suggested that prescription decisions may be influenced (descending order of relevance) by pharmaceutical promotion, order-of-entry of drugs in the market, drug price, drug characteristics and place (distribution). The magnitude in terms of relevance is shown in table 4.1.

Table 4.1 – Marketing relevance of marketing factors

Marketing categories	**n**
Promotion	97
Order of market entry	93
Price	25
Product	16
Place (distribution)	5

Source: adapted from Stros & Lee (2015)

More recently, Murshid & Mohaidin (2017) proposed a model of physician prescribing decisions derived from the theory of persuasion, the agency theory, the theory of the planned

behavior, and the social power theory. Their model includes marketing efforts, patient characteristics and pharmacists' factors explaining physicians' decisions to prescribe drugs, as shown below in figure 4.3.

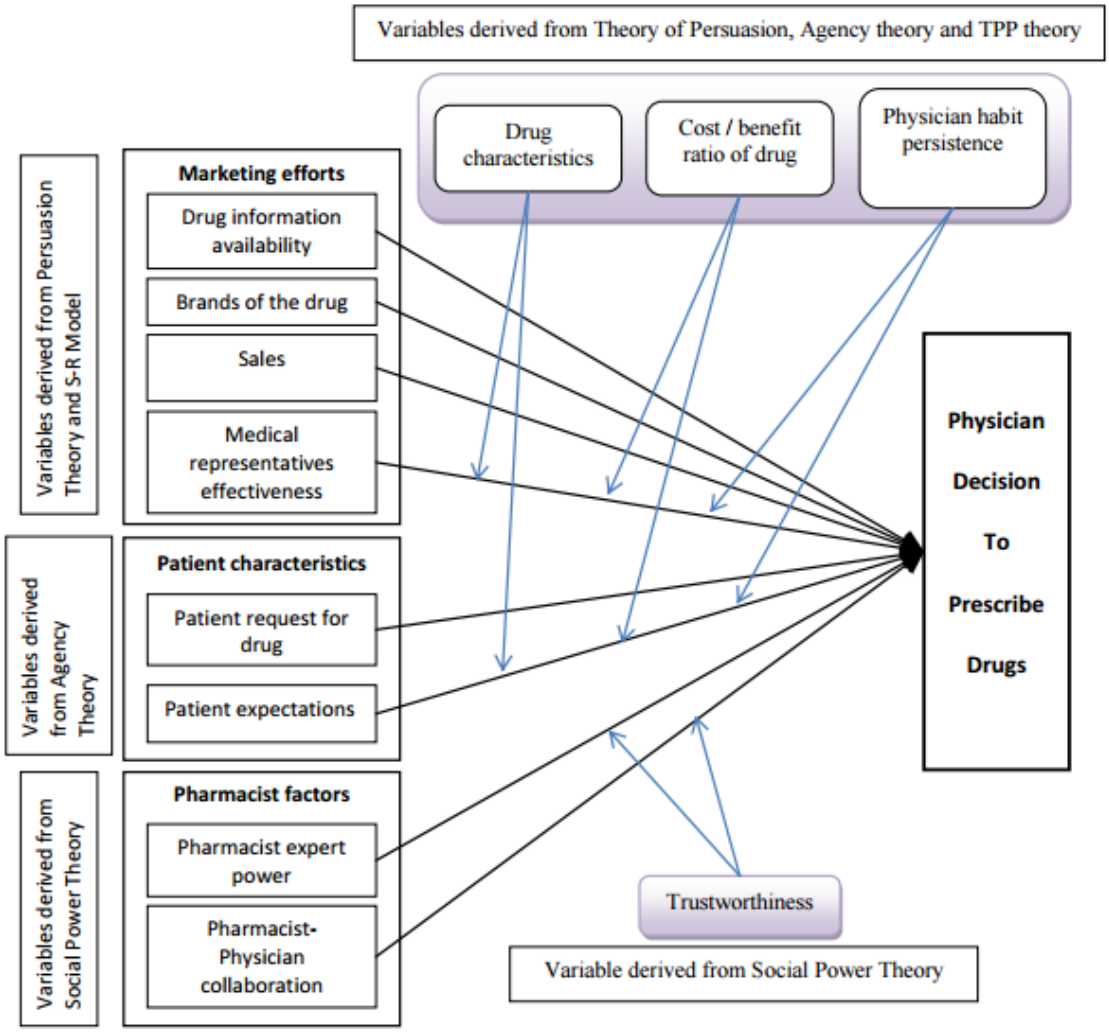


Figure 4.3 - Murshid & Mohaidin proposed model of physician prescribing decision

Source: Murshid & Mohaidin (2017)

Murshid & Mohaidin (2017) model appears however to lack additional variables explaining physician prescription decisions, as for instance regulation, and other variables related to physicians and their profession, and additional marketing-related activities.

Based on the literature review, several other factors were identified, which we organized into two categories: non-marketing related and marketing-related factors. Regarding the former, these can be framed into a physicians and their profession scope, to a market scope, to a regulatory and institutional scope, and to patients' scope. The marketing-related factors can be

framed into product scope, promotion scope, pricing scope and distribution scope. A description of those factors will now be presented.

Non-marketing related

- **Physician and profession**

Pitt & Nel (1988) found that the most influential prescription decision determinants, based on physicians' opinions, are experience with the product, and informal discussions with colleagues. Spiller & Wymer (2001) noted that «*physicians primarily choose patient medications based on their personal preferences and prior experience with drugs (…) also rely upon drug compendiums and medical journals*» (p. 102), and that apparently advertising may not evidence a substantial influence. Spiller & Wymer (2001) also studied what were the information sources that appeared to influence physicians' drug choices when prescribing. They found that the most declared influential factors in physicians' prescription choices were previous experience (with a category mean of 3,6 out of 4) and physician experience (3,4). Pitt & Nel (1988) highlighted scholarly articles by specialists in scientific medical journals as a declared source of influence do doctors, in the scope of their prescription decisions. Key opinion leaders may influence doctors' prescribing decisions, given their credibility among colleagues, behaving many times as instructors to their colleagues, speakers at meetings, and senior editors of textbooks (Meffert, 2009), impacting their colleagues' prescribing habits.

Switching costs may be another influence to physicians' prescription decisions. According to Bain (1956), buyers may prefer to choose already established products over new ones, which may benefit incumbent firms, while new entrants may have to decide a lower price, or higher promotion costs. This may be related to consumer switching costs, since new entrants have to persuade consumers to switch for their brand (Stros & Lee, 2015). Porter (1980) had defined switching costs as «*one-time costs facing the buyer of switching from one supplier's product to another's*» (p. 10), suggesting that switching costs raise barriers to entry. These switching costs addressed by Porter (1980) included employee retraining costs, cost of new ancillary equipment, cost and time in testing or qualifying a new source, need for technical help as a result of reliance on seller engineering aid, product redesign, or psychic costs of severing a relationship. More than two decades after, Burnham, Frels & Mahajan (2003) proposed three higher order types of switching costs: procedural (economic risk costs, evaluation costs, set

up costs, and learning costs), financial (benefit loss costs, and monetary loss costs), and relational (personal relationship loss costs, and brand relationship loss costs).

Campo et al (2006) suggested that a high level or inertia or resistance may be present in prescription decisions, both for a group of products, and for specific patients. Coscelli (2000), when analyzing the empirical factors determining individual physicians' and patients' choices among a group of equivalent drugs, suggested that physicians' prescriptions evidence habit persistence. By other words, he proposed that time dependence make prescribers far from indifferent from any point in time (p. 367). Reciprocity is another factor influencing physicians' prescription behavior. According to Cialdini (1984), we are obligated to the future repayment of favors, gifts, and invitations. Roughead, Harvey & Gilbert (1998) noted that the reciprocity principle was present regarding PSRs offers of drug samples, gifts, printed material, patient information leaflets and invitations. Physicians may feel obligated to reciprocate PSR regular assistance and free meals by increasing the likelihood of prescribing the drug brands they promote. Katz, Caplan and Merz (2010) also referred the reciprocity rule, where physicians may feel «*compelled to reciprocate by supporting their benefactors' products*» (p. 10).

- **Market**

Order-of-entry in the market may also significantly impact prescription decisions. Kremer et al (2008), in their review on the effectiveness of pharmaceutical promotional expenditures, suggested that the «*pharmaceutical market is characterized by strong order-of-entry effects, creating barriers for new entrants*» (p. 235). Kalyanaram (2008), studying three therapeutic classes of drugs, from both prescription and over-the-counter markets, found a significant order of entry effect on market share.

- **Regulatory and institutional**

Clinical guidelines and drug formularies may impact physicians' prescription patterns. Guidelines main goal is to help prescribers select appropriate therapies for specific health conditions (Aronson, 2006). As an example from the United Kingdom, the NHS West Essex Clinical Commission Group defined clinical guidelines' aim as to «*address the whole medical management of a particular therapeutic area for example, osteoporosis, asthma etc*» (UK NHS West Essex Clinical Commission Group (2017)). As proposed by Huskamp, Epstein & Blumenthal (2003), drug formularies are «*lists of drugs that are preferred by a health plan or employer*» (p. 149). They distinguish three types of formularies, in the scope of the financial

incentives for prescribing medicines that are included in the list: the first type are known as open formularies, which have a more educational role; the second type are known as closed formularies, where a compulsory list of medicines is available for specific pathologies of the patients (exceptions may however apply, given that physicians are authorized a waiver for very specific patient situations); and a third type, as intermediate one (intermediate arrangement), which, as noted by Huskamp, Epstein & Blumenthal (2003), is an incentive formulary which offers financial incentives for patients (less expensive drugs) and their physicians, by having characteristics of both previous types, in the sense that, by the one hand, they are compulsory in nature, and by the other hand, they allow for a certain level of coverage or acceptance of non-preferred of non-listed drugs.

According to the Academy of Managed Care Pharmacy (AMCP), a «*drug formulary, or preferred drug list, is a continually updated list of medications and related products supported by current evidence-based medicine, judgment of physicians, pharmacists and other experts in the diagnosis and treatment of disease and preservation of health. The primary purpose of the formulary is to encourage the use of safe, effective and most affordable medications*» (AMCP, 2017). A similar definition is proposed by UK NHS West Essex Clinical Commission Group (2017), defining prescription formulary as «*a list of medicines from the British National Formulary (BNF) which have been approved for prescribing by MOPB. The aim of MOPB is to promote rational evidence-based and cost-effective prescribing within West Essex health economy*».

As highlighted by Huskamp, Epstein & Blumenthal (2003), drug formularies may achieve cost savings in two main ways. The first, by allowing patients to be prescribed less expensive drugs or higher copayments. The second, by allowing a higher bargaining price of public and private health providers when negotiating with drug manufacturers, stimulating price competition. Huskamp, Epstein & Blumenthal (2003) also suggest that closed formularies, given their essentially compulsive scope, usually result in directing the «*volume of prescriptions among competing products (or in industry jargon, "move market share") according to price and thus extract larger price discounts from manufacturers*» (p. 150). Clinical guidelines, and especially drug formularies, may therefore impact physicians' prescription patterns, especially the second as it may assume, in closed formularies, a compulsive character in its observation of a specific drug list available for prescription by physicians. Schumock et al (2004) research confirmed that formulary status was the third most influencing factor in the drug prescription choice.

Drug prescription policies can have an effect on prescription behavior, as noted by Schumock et al (2004). These restrictions can be of different types. As noted by Fischer, Koch, Kostev & Stargardt (2017), physician prescription budgets can contain pharmaceutical spending, as the most direct way of interceding in the prescribing process, limiting the total number of prescriptions issued by a physician (Stremersch & Lemmens, 2009). Prescription budgets can influence doctors to choose brands more selectively and to increase the generic share on prescriptions (Fischer et al, 2017). Restriction on direct-to-consumer advertising can also have impact on prescription behavior, even if physicians are not the targets of this type of promotion. Stremersch & Lemmens (2009) found that countries prohibiting DTCA have significantly lower sales on new drugs when compared to countries where DTCA is allowed.

Regulation of marketing efforts to physicians also impacts prescription behavior. Stremersch & Lemmens (2009) suggested that the impact of restricting pharmaceutical marketing efforts pharmaceutical manufacturers develop with physicians tends to have a negative effect on sales, although the coefficient obtained was non-significant. King & Bearman (2017) found that the uptake of new expensive medications was significantly lower in US states with marketing regulation, versus in states with unrestricted pharmaceutical marketing. These regulations and their effects will be more deeply analyzed in chapter 6. Mandatory generic substitution can also have a significant impact on physician prescription behavior. Andersson, Petzold, Allebeck & Carlsten (2008) studied the impact of the implementation of a mandatory generic substitution program in Sweden, and found that sales of substitutable pharmaceuticals evidenced proportionally larger growth when compared against sales of non-substitutable pharmaceuticals (that is, drugs that do not have yet generics competing against), suggesting that the impact of the substitution program was significant and positive in terms of sales growth of less expensive prescription options.

Drug reimbursement, in the sense that patients can pay a lower value for their medicines, can have an impact on physician prescription behavior, as addressed by Spiller & Wymer (2001).

- **Patients**

Drug requests from patients – either influenced by DTCA as noted above, or by other source of influence -, can influence prescription behavior. Kravitz et al (2005) noted that physicians

may accept, in some occasions, to prescribe the drug requested by the patients. This evidence had already been addressed by Mintzes et al (2002), where they stated that «*patients' requests for medicines are a powerful driver of prescribing decisions*» (p. 279). Patient and prescription situation (either routine or non-routine) may also influence physician prescription behavior, according to Campo et al (2006), who concluded that while for routine situations physicians prefer to trust their own experience and knowledge on a limited number of drugs for each specific situation, for non-routine situations involving new patients with a complex profile regarding pathologies physicians tend to observe a more extensive evaluation, using multiple criteria.

Marketing related

- **Product**

Drug efficacy is one of the factors impacting physician prescription behavior, as highlighted by Gönül et al (2001). Schumock et al (2004), using a questionnaire administered to physicians, clinical pharmacists, and formulary committee members, found that the factors considered as most influential in prescribing decisions were, to all three types of health care practitioners participating in the research, drug safety and drug effectiveness. Drug characteristics such as effectiveness and side effects can moderate the effect of detailing in prescription behavior, as demonstrated by Venkataraman & Stremersch (2007).

Stros and Lee (2015) highlighted the importance of product design as a key role for successful marketing, since it is appears to be a determinant of the sales success of both early and later market entrants. As key pharmaceutical product attributes, they highlight the innovativeness, the quality, the branding and, to a much lesser extent, the packaging, underlining two product design strategies that may be useful, whether applied to early or to late entrants in a pharmaceutical market: while for an early entrant product innovation appears to be the main aspect, for a later entrant it may be more beneficial to stress the product differentiation. Pitt & Nel (1988) noted that ease in remembering the brand name was one of the reasons doctors underlined as influencers of their prescription decisions (though much less influential than promotion activities). Fischer, Leeflang & Verhoef (2010) demonstrated that product quality can have a very strong effect on height-of-peak-sales, while reducing the time-to-peak-sales.

- **Price / cost**

According to Stros & Lee (2015) review, pricing occupies the third place in terms of relevance of the marketing factors in the prescription pharmaceutical industry. Physicians are mostly price sensitive, when comparing the impact of price with other aspects such as drug efficacy and patients' conditions (Gönül et al, 2001). Price sensitivity – measured as price elasticity - seems to decrease in the presence of promotional activities such as detailing (Rizzo, 1999; Windmeijer et al, 2006). Spiller & Wymer (2001) underlined that affordability (such as cost of drug, insurance possession, and reimbursement) is one of the factors impacting physician prescription behavior. Pitt & Nel (1988) also noted that drug price to the patient influences doctors' decision on which drug to prescribe.

Prescription drugs price is one of the most regulated marketing instruments and will be further addressed in this thesis.

- **Promotion**

Promotion is the most relevant marketing dimension in pharmaceutical marketing, in terms prescription decisions (drug sales), as highlighted by Stros and Lee (2015), while also suggesting that pharmaceutical promotion serves at least two functions: one consists of habit formation, and other consists of information provision.

The most important promotion tool in terms of pharmaceutical marketing, both in terms of volume (IMS Health, 2015a) and in terms of influence (Berndt, Bui, Reiley & Urban, 1995; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004), is detailing through PSRs. The study of the importance of detailing has been made not only by quantitative research using time series (such as the authors now listed), but also by quantitative detailing using cross-sectional studies. Among these, we find Pitt & Nel (1988), Andaleeb & Tallman (1996), Schumock et al (2004), and Spiller & Wymer (2001), to list a few. Pitt & Nel (1988), in their research involving physicians' perception of promotion instruments influence on their prescribing decisions, noted that, of promotion tools, sales calls (detailing) were considered by doctors as the most influential. Andaleeb & Tallman (1996) confirmed that physicians saw PSRs as an important source of information, but also considering they could access information using other information sources without PSRs' support. Schumock et al (2004), using a questionnaire administered to physicians, clinical pharmacists, and formulary committee members, found that physicians scores on face-to-face detailing as an influencing factor averaged only 3,15 on a zero (no influence) to five (the greatest amount of influence)

Likert scale, scoring 17th most influential in a total of 31 factors evaluated. Spiller & Wymer (2001), in their research, found that advertising (which includes PSRs activities) scored the lowest average (1.8) among all promotion initiatives listed in their questionnaire.

Drug sampling (Parsons & Abeele, 1981; Fugh-Berman & Ahari, 2007; Chimonas, Brennan & Rothman, 2007) and gifts and meals (Katz, Caplan & Merz, 2010; King & Bearman, 2017; DeJong et al, 2016) are other promotion instruments that have been demonstrated to have impact on physicians prescription behavior. E-detailing, despite relatively scant literature available, has also been demonstrated to influence prescription behavior, as noted by Gönül & Carter (2010). Pharmaceutical promotion, including detailing and other promotion instruments (both traditional and digital) will be further developed in higher detail later in this thesis. Direct-to-consumer advertising can also have an impact on physicians' prescription behavior, as noted by Kravitz et al (2005). They found that patients' requests to physicians have a strong effect on physician prescribing, influencing their choices for prescription drugs. Seminars, conferences and lectures may impact physicians' prescription choices too, as noted by Pitt & Nel (1988). These researchers also highlighted the credibility and reputation of the company as an influential factor of prescribing decisions.

It is interesting to note that, by the one hand, empirical studies evaluating the impact of pharmaceutical promotion in prescription behavior using quantitative datasets (drug sales or prescriptions vs promotion investments) typically point to positive impact on drug sales, whereas studies directly addressing physicians with questionnaires generally appear to point to a small effect of pharmaceutical promotion in prescription decisions. These surveys administered to physicians, explicitly asking them for their opinion, may not represent the real influence magnitude of the impact on their prescription decisions.

- **Distribution**

Stros & Lee (2015) studied the relevance of marketing dimensions on prescription drugs and found that distribution is the least relevant marketing mix component. They suggested that the role of distributional marketing policies do not appear to represent a significant role in pharmaceutical success. Product availability at the point of sale appears however to be a relevant factor impacting physicians prescription decisions, as noted by Dimaculangan (2011), allowing physicians' clients (patients) place and possession utilities through the distribution channel. This evidence had already been noted by Pitt & Nel (1988), where they

suggested that doctors recognized product availability as one of influencing factors of their prescribing decisions (though much less influential than promotion activities).

Table 4.2 summarizes the factor influencing prescription behavior, compiled after the literature review. The division in marketing and non-marketing related is aimed at facilitating the interpretation of the multiple influences on prescription behavior, as a very complex process. It is not intended to be, however, a hermetic separation, since there are many interactions between the two groups. As a first example, pricing / cost is related to regulatory and institutional (drug reimbursement). As a second example, promotion is related to physician and profession (promotion impacts reciprocity).

Table 4.2 – Factors influencing physicians' prescription behavior

	Scope	Influencers of physician prescription behavior of prescription drugs	Theoretical grounding (non-exhaustive)
Non-marketing related	Physician and profession	Personal preferences and prior experience with drugs	(Spiller & Wymer, 2001)
		Experience with the product, and informal discussions with colleagues	(Pitt & Nel, 1988; Spiller & Wymer, 2001)
		Drug compendiums and medical journals	(Pitt & Nel, 1988; Spiller & Wymer, 2001)
		Switching costs / state of dependence, leading to a habit formation	(Coscelli, 2000; Campo et al, 2006; Stros & Lee, 2015)
		Reciprocity (to pharmaceutical sales representatives)	(Cialdini, 1984; Roughead, Harvey & Gilbert, 1998; Katz, Caplan & Merz, 2010)
		Key opinion leaders	(Moynihan, 2008; Meffert, 2009)
	Market	Order of entry in the market	(Kalyanaram, 2008; Kremer et al, 2008)
	Regulatory and institutional	Formulary status and drug prescribing restriction policies	(Spiller & Wymer, 2001; Schumock et al, 2004)
		Clinical guidelines	(Aronson, 2006)
		Drug formularies	(Huskamp, Epstein & Blumenthal, 2003)
		Drug reimbursement	(Spiller & Wymer, 2001)
		Mandatory generic substitution	(Andersson, Petzold, Allebeck & Carlsten, 2008)
		Physician prescription budgets	(Stremersch & Lemmens, 2009; Fischer, Koch, Kostev & Stargardt, 2017)
		Restrictions on direct-to-consumer advertising	(Kravitz et al, 2005; Stremersch & Lemmens, 2009)
		Restrictions on pharmaceutical marketing efforts to physicians	(Stremersch & Lemmens, 2009; King & Bearman, 2017)
	Patients	Patients' requests	(Mintzes et al, 2002; Kravitz et al, 2005)
		Routine vs non-rountine patient and situation	(Campo et al, 2006)
Marketing related	Product	Drug safety / side effects, drug efficacy / effectiveness	(Gönül et al, 2001; Schumock et al, 2004; Venkataraman & Stremersch, 2007)
		Product (innovativeness, quality, branding and packaging)	(Fischer, Leeflang & Verhoef, 2010; Stros & Lee, 2015)
		Ease in remembering the product brand name	(Pitt & Nel, 1988)
	Promotion	Pharmaceutical promotion in general	(Stros and Lee, 2015)
		Credibility and reputation of the company	(Pitt & Nel, 1988)
		Direct-to-consumer advertising	(Kravitz et al, 2005)
		Detailing and competitive detailing	(Pitt & Nel, 1988; Berndt, Bui, Reiley & Urban, 1995; Spiller & Wymer, 2001; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004; Schumock et al, 2004)
		Drug sampling	(Parsons & Abeele, 1981; Spiller & Wymer, 2001; Chimonas, Brennan & Rothman, 2007; Fugh-Berman & Ahari, 2007)
		Gifts and meals	(Katz, Caplan & Merz, 2010; King & Bearman, 2017; DeJong et al, 2016)
		E-detailing	(Gönül & Carter, 2009)
	Pricing / cost	Drug price, patient's financial situation / conditions, insurrance coverage	(Pitt & Nel, 1988; Gönül et al, 2001; Spiller & Wymer, 2001; Stros & Lee, 2015)
	Distribution	Drug distribution / product availability	(Pitt & Nel, 1988; Dimaculangan, 2011; Stros & Lee, 2015)

Source: own elaboration

4.5.Chapter synthesis of main findings

Chapter 4 addressed literature on physicians and medical prescription. Some main conclusions were gathered from the study of theories on these fields. Despite the existence of

some medical professionals (including physician assistants, and nurses) that have limited prescription privileges in some countries, physicians are the main medical professional with the statutory authority and privilege to write prescriptions of prescription-only drugs, making them the main deciders in the buying decision process of prescription drugs, controlling more than four fifths of health care expenditures. Physicians have a series of roles in the pharmaceutical industry, including medical prescription, communication with patients, and increasing responsibilities for the management of human and financial resources in health care, especially in hospital settings. Physicians can be generally classified as generalists (family and primary care doctors), or specialists. While the first typically provide continuing and comprehensive medical care to individuals, families and communities, but without a specific specialization in terms of therapeutic areas, the second generally specialize in providing medical care in the scope of certain diseases, types of patients and methods of treatment, acting also as educators and consultants to generalists.

Drugs can be prescription-only, when a medical prescription is needed, written by a physician or other medical professional with the authority to do so, or non-prescription (OTC), which does not require a medical prescription and can be bought directly by patients in retail pharmacies. In the last two decades, with the advent of the internet and with the digitalization of many processes in health care, electronic prescription has been implemented by health tutelage as a means to contribute to better prescription practices. Clinical decision support systems also have been applied, consisting of computer-based algorithms that assist clinicians in the diagnostic and prescription process, helping them minimize errors (including adverse drug events), and contributing to improve patient outcomes.

Physicians' prescription choice is a very complex and sensitive process, which can be influenced by several factors. The review that was performed allowed the classification of these factors in two groups: non-marketing related, and marketing related. Non-marketing related factors can then be divided in physicians and their profession scope (including the influence of physicians' personal preference and personal experience with a drug, informal discussions with other physicians, drug compendiums, physicians' state of dependency and switching costs given the habit formation, and physicians' reciprocity toward PSRs visits, drug samples, and gifts and meals), market scope (drug order of entry in the market, where drugs launched first typically create barriers to new entrants), regulatory and institutional scope (including drug reimbursement typology, formulary status and drug prescription policies, clinical guidelines, drug formularies, mandatory generic substitution and physician

prescription budgets, intended to directly affect prescription decisions through a variable degree of enforcement, and restrictions on direct-to-consumer advertising and on pharmaceutical marketing efforts to physicians, intended to indirectly condition physicians' prescription behavior), and patients' scope (where patients' requests for specific drugs may influence physicians to prescribe them, and patient and prescription situation, either routine or non-routine, may also influence physician prescription behavior).

Marketing related factors can be divided in product scope (including drug safety and effectiveness, physician perception on product innovativeness, quality, branding and packaging, and drug efficacy), promotion scope (including DTCA, detailing, drug sampling, gifts and meals and e-detailing, all shown to influence physicians' prescription behavior), pricing scope (including physicians' perception on drug prices, evaluation of patient financial situation and patient possession of insurance coverage), and distribution scope (where product availability at the point of sale appears to be an important factor impacting physicians prescription decisions).

Figure 4.4 below illustrates and summarizes these factors influencing medical prescription.

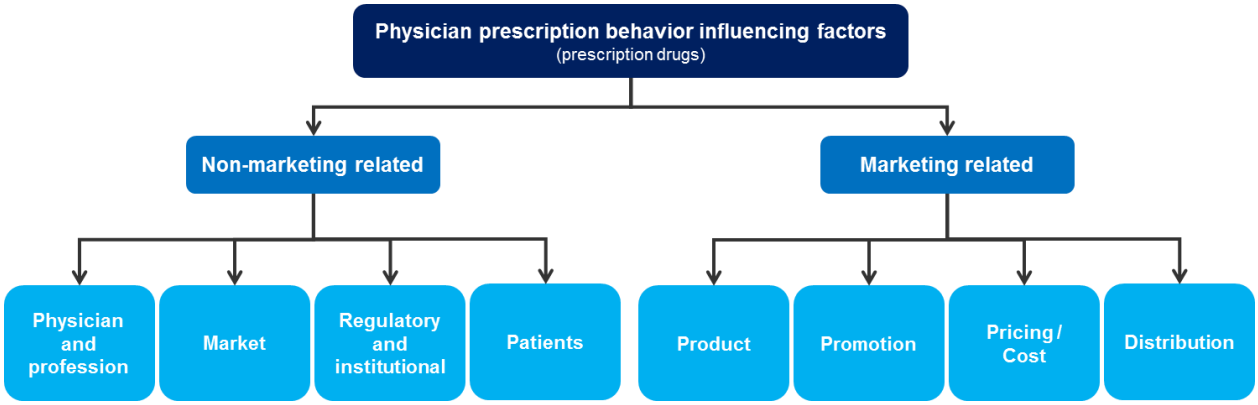


Figure 4.4 – Physician prescription behavior influencing factors

Source: own elaboration

5. Pharmaceutical industry promotion

5.1.Content and logic of the chapter

This chapter addresses the theories on pharmaceutical industry promotion of prescription drugs to physicians and is aimed at providing a theoretical framework where detailing is rooted.

The chapter starts by addressing the main concepts in the scope of pharmaceutical industry promotion. It then addresses marketing communication as a process to deliver messages from senders (pharmaceutical manufacturers) to receivers (pharmaceutical stakeholders). The chapter then follows with the analysis of communication channels and promotion tools, underlining their differences and interactions. In this topic, several classifications of communication channels and promotion tools are addressed, and a summary table is presented to help understand these concepts. The concepts of multichannel marketing and omnichannel marketing are also explained. The chapter then approaches promotion tools using traditional communication channels, with the analysis of each tool and a special focus on detailing, given the specific theme of this thesis. Detailing is analyzed in higher detail, with the presentation of a series of theoretical generalizations that were compiled through the analysis of reference literature from the last decades, and mainly from the last 15 years. It follows with promotion tools using digital communication channels – more recent tools that appeared after the development of information technologies and the advent of the World Wide Web – with a particular focus on e-detailing.

The chapter also addresses the magnitude of investments made by pharmaceutical manufacturers, and approaches additional perspectives on pharmaceutical marketing, highlighting stakeholders perspectives on pharmaceutical marketing directed at physicians, push versus pull promotion, physicians preference and prescription attitude on digital communication channels. It also addresses promotion activities effectiveness, and discusses ethical considerations related to pharmaceutical promotion of prescription drugs to physicians.

The chapter ends with a synthesis of the main findings, where a summary of the most relevant aspects of the literature review on pharmaceutical marketing will be highlighted.

5.2.Concepts

Pharmaceutical promotion represents one of the marketing mix dimensions pharmaceutical manufacturers use to interact with stakeholders. Given the scope of this thesis, a higher detail

will be given to pharmaceutical promotion. Promotion expenditures (of which detailing is the most important instrument) can not only impact physician prescription behavior, but also can have an impact on the sales behavior of the promoted drugs in terms of its peak. Fischer, Leeflang & Verhoef (2010), in their research where they studied calcium channel blockers and ACE inhibitors (antihypertensives) in four European markets, found that promotion expenditures (detailing, which represented more than 90 per cent of the total, but also journal advertising and direct mailing) can increase the level of peak sales of a drug (historical sales maximum), while also decreasing the time-to-peak-sales (time between the beginning of the drug commercialization and peak sales).

Pharmaceutical industry promotion is generally limited to drugs on patent and can be classified as direct-to-physician promotion (DTPP) or direct-to-consumer advertising (DTCA), as noted by Datta & Dave (2016).

Pilarczyk (2011) addressed pharmaceutical promotion in the light of Kotler, Keller, Brady, Goodman & Hansen (2009, p. 762) classification of marketing tools, dividing it in advertising (specialist press publications addressed to physicians and pharmacists, leaflets), personal selling (pharmaceutical sales representatives), sales promotion (free samples of drugs for physicians, discounts for wholesale purchases, package deals for pharmacies, loyalty programs), public relations (marketing events, training for doctors and pharmacists, lobbying, sponsorship, media relations, consulting programs for pharmacies), and e-pharma marketing.

Pharmaceutical manufacturers use promotion tools to interact with their stakeholders, through communication channels.

Pharmaceutical marketing interactions can occur not only after physicians' graduation, but before too. Pharmaceutical sales representatives detail medical students and offer gifts (Sarikaya, Civaner & Vatansever, 2009; Austad et al, 2013), books (Wazana, 2000) and meals (Austad et al, 2013). The interactions appear to continue during medical internships and training, as demonstrated by Zipkin & Steinman (2005) and Riese et al (2014).

Pharmaceutical manufacturers use a variety of promotion tools to impact and interact with their clients, mainly physicians. Promotion tools using traditional communication channels include detailing, drug sampling, and advertising in professional journals (Datta & Dave, 2016), gifts, conference travel, paid meals, PSR speakers, in the scope of continuing medical education (CME) funding and event sponsorship, and research funding (Wazana, 2000), direct mail (Parsons & Abeele, 1981), constituting what Datta & Dave (2016) classified as DTPP.

Promotion tools using traditional channels also include direct-to-consumer advertising, or DTCA (Iizuka & Jin, 2005), given the non-digital part of it. Promotion tools using digital communication channels include e-detailing (Alkhateeb & Doucette, 2008), e-sampling (Kumar & Panigrahi, 2014), company websites and healthcare portals (Puschmann & Alt, 2001), health social networks (Swan, 2009), e-mailing (Pedroso & Nakano, 2009), online continuing medical education (Wutoh, Boren & Balas, 2004), and e-Direc-to-consumer advertising in the scope of Web 2.0 (o'Reilly, 2005).

5.3.Marketing communication

Pharmaceutical manufacturers communicate with several stakeholders in the pharmaceutical industry. These include physicians, pharmacists, nurses, wholesalers, payers (both public and private) and patients. Companies use several promotion tools through communication channels to interact with the stakeholders, mainly physicians. Figure 5.1, adapted from the one proposed by Pilarczyk (2011), evidences this communication process in the pharmaceutical market.

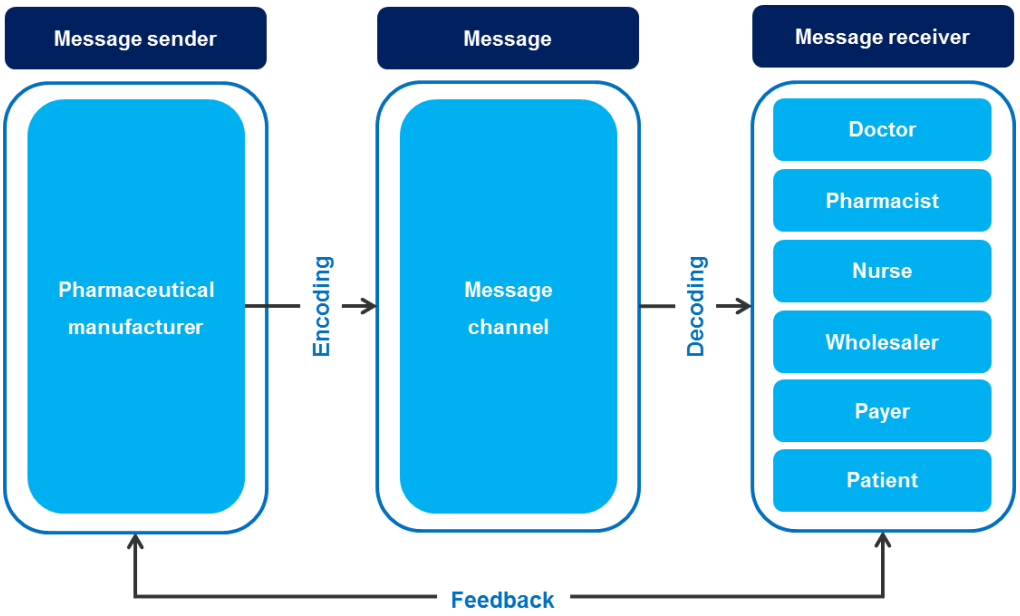


Figure 5.1 – Marketing communication process in the pharmaceutical market

Source: adapted from Pilarczyk (2011)

5.4.Communication channels and promotion tools

The literature on pharmaceutical marketing does not appear to explicitly separate the concepts of communication channels and promotion tools. Some scholars seem to address interchangeably the two concepts in the same article, as for instance Pilarczyk (2011), when

proposing a framework that combined, in a table format, promotion tools and forms, and communication channels. Bernewit (2001) also appeared to address interchangeably communication channels and promotion tools, when discussing the trade-offs between in the selection of promotion tools and resource optimization of the communication mix. Auruskeviciene, Butkeviciene & Salciuviene (2015), when approaching communication channels in the pharmaceutical industry, referred pharmaceutical sales representatives' visits (detailing), conferences, and dedicated websites as communication channels. However, these can be considered, instead, promotion tools or instruments. Rod & Saunders (2009), in their article addressing the informative and persuasive components of pharmaceutical promotion, listed direct-to-consumer advertising, detailing and conferences as promotion channels, but they most likely should be considered promotion tools.

5.4.1. Definitions

Given this apparent lack of clear differentiation between communication channels and promotion tools, we propose clarification by attempting to delineate a concept perimeter, and the relations between the two concepts. Analyzing Kotler & Armstrong (2012) approach, communication channels can be defined as the means through which the message moves from the sender to the receiver. Therefore, communication channels may be interpreted as the vehicles that make possible the usage of the promotion tools, or the agents that allow the message to be carried from the sender to the receiver. In the scope of the pharmaceutical industry and its promotion of prescription drugs, communication channels include face-to-face, television, telephone (both fixed and mobile), online (including e-mail, websites, social media), print, and mail.

Promotion tools definition appears naturally, as instruments used by companies to develop interaction with clients and reach promotion goals, using communication channels. Kotler & Armstrong (2012) explained that companies use a specific blend or combination of promotion tools, to convincingly communicate customer value and build relationships with customers, and this specific blend is called the promotion mix. They also noted that companies need to deliver a «*clear, consistent, and compelling message about its organization and its brands*» (p. 406). Promotion tools used by pharmaceutical manufacturers include detailing, e-detailing, direct-to-consumer advertising, drug sampling, e-sampling, gifts and meals, mailing, e-mailing, continuing medical education (both off and on-line), medical journal advertising, medical social networks, health care portals, and other, later discussed in this thesis, exploring the theoretical framework for each tool.

5.4.2. Classifications

It is also of interest to understand how communication channels are classified. Kotler & Armstrong (2012) classified communication channels as personal, or non-personal. They explained that personal communication channels are «*channels through which two or more people communicate directly with each other, including face-to-face, on the phone, via mail or e-mail, or even through an internet "chat"*» (p. 419), deriving their effectiveness through individualized presentation and feedback (Kotler et al, 2009). Conversely, nonpersonal communication channels are, as proposed by Kotler & Armstrong (2009), «*media that carry messages without personal contact or feedback. They include major media, atmospheres, and events. Major media include print media (newspapers, magazines, direct-mail), broadcast media (television, radio), display media (billboards, signs, posters), and online media (e-mail, company Web sites, and online social and sharing networks). Atmospheres are designed environments that create or reinforce the buyer's leanings toward buying a product (…) Events are staged occurrences that communicate messages to target audiences. For example, PR departments arrange grand openings, shows and exhibits, public tours, and other events*» (p. 419).

Williams & Hensel (1990) had already addressed the distinction between the personal and nonpersonal nature of the information source, underlining the fact that personal interaction may occur or not. Personal sources include face-to-face (personal selling through detailing, and events such as conventions and meetings), and nonpersonal sources include print. Communication channels can also be traditional, or alternative (electronic and mobile-based), as noted by Auruskeviciene, Butkeviciene & Salciuviene (2015). Alternative channels are also called as digital or electronic channels (Katsanis, 2015). Gibson (2014) also differentiated between traditional (such as print and television) and digital (such as the internet) channels. Auruskeviciene, Butkeviciene & Salciuviene (2015) explained that the main traditional communication channel used by pharmaceutical companies is face-to-face personal selling through pharmaceutical sales representatives. They also explained that electronic and mobile-based communication channels have become more popular tools. Pilarczyk (2011) precised that these new (digital) communication channels are typically interactive and allow contacts regardless of distance.

It is also of relevance to understand how promotion tools have been classified in previous research. Williams & Hensel (1990) analyzed the findings of many studies on pharmaceutical marketing to describe the sources and importance of several promotion instruments in

physicians' prescription choices. After identifying the main promotion tools covered in the literature, they classified them in commercial and non-commercial. Commercial instruments include direct mail, journal advertising, detailing (personal selling), and sampling, whereas noncommercial instruments include journal articles, colleagues (peers), pharmacists, conventions, and meetings. Using this framework from William & Hensel (1990), the more recent promotion instruments can also be classified as commercial or noncommercial, which will be presented in table 5.1. Williams & Hensel (1990) also used another classification for promotion instruments: marketer-controlled sources and non-marketer-controlled sources. The former include direct mail, medical journals, detailing and sampling, and the latter include journal articles and popular press articles.

5.4.3. Single, multi and omnichannel marketing

While single channel marketing consists of the usage of one communication channel to interact with customers, multichannel marketing, according to Rangaswamy & Bruggen (2005), allows companies to build long-term customer relationships by «*simultaneously offering their customers and prospects information, products, services, and support (or any combination of these) through two or more synchronized channels*» (p. 6). Katsanis (2015) proposed a multichannel definition in the scope of the pharmaceutical industry, as the use of more than one communication channels to reach a target audience, in the case, primarily the physician audience. She noted that multichannel includes both traditional and electronic channels. Pharmaceutical companies use multichannel approach by using several communication channels to impact physicians. For instance, ZS (2014b) report referred a very simple example where a pharmaceutical company may start with a PSR detail to doctors (face-to-face channel), followed by an e-mail with on-line sampling offer (on-line channel). The advent and growth of multichannel marketing in the pharmaceutical industry does not necessarily imply a reduced importance of the PSR. Capgemini (2013) research concluded that more than five out of ten (52%) doctors consider that PSRs' roles will evolve into a coordinator or director of multichannel information sources.

Kotler & Armstrong (2012) explained that communication channels must be integrated and coordinated by companies to «*deliver a clear, consistent and compelling message about the organization and its products*» (p. G4), calling this the integrated marketing communication, or IMC. Kotler & Armstrong (2012) noted that companies communicate with customers using a variety of channels, but the message must be consistent and coherent across channels, avoiding conflicting or blurred messages. They also explained that under a IMC approach

marketers must carefully manage all touchpoints where customers may interact with the company and its brands. In the scope of the prescription drugs promotion, there is the need of carefully manage the messages conveyed through all communication channels that were chosen to interact with physicians, either face-to-face, mail, television, on-line, telephone, or printed media, where each contact opportunity must deliver a positive and consistent message, image and experience.

This integrated marketing experience addressed in the previous paragraph is related to another concept called omnichannel. Kotler, Kartajaya & Setiawan (2016) explained that omnichannel involves the usage of both online and offline channels to interact with customers, regardless of touchpoints, which can include face-to-face points of contact, online (applications and websites), telephone (call center), or other channels. They explained that, more than impact customers with many touchpoints, omnichannel is aimed at allowing customers to have a hassle free, seamless and consistent experience when moving from one channel to another, by developing a concerted effort across multiple online and offline channels. Omnichannel marketing uses data to optimize channel operations, by learning where customers spend their time and how they react to different channels and promotions, allowing marketers to tailor specific messages to each individual customer, as noted by Kotler, Kartajaya & Setiawan (2016). They also underlined that, by using this type of customer-related data, marketers can predict what customer will buy in future moments. In this scope, and considering the pharmaceutical industry, closed loop marketing (CLM) - previously addressed in this thesis - is a concept related to multichannel and to omnichannel marketing, since CLM can integrate the utilization of multiple channels such as on-line (websites and social media), added to detailing (face-to-face), helping companies to close the loop in the process of information provision to physicians (Katsanis, 2015). Vechhione (2008) had already highlighted the link between CLM and multichannel, underlining that CLM «*is the ability to use multichannel communications to drive several channels to create interactions with customers and to get a better understanding of what their needs are*» (p. 41).

5.4.4. Linking communication channels and promotion tools

Pharmaceutical promotion tools can therefore use personal and non-personal, traditional and digital communication channels. We will now explore are the most relevant promotion tools for each communication channel.

Personal communication channels include face-to-face personal selling (Kotler & Armstrong, 2012; Auruskeviciene, Butkeviciene & Salciuviene, 2015), phone, mail, e-mail and internet

chat when communicating directly (Kotler & Armstrong, 2012). Nonpersonal communication channels include television, print media, on-line (e-mail when not communicating directly, websites, and online social and sharing networks), and events (Kotler & Armstrong, 2012; Pilarczyk, 2011).

Traditional communication channels include face-to-face personal selling (Auruskeviciene, Butkeviciene & Salciuviene, 2015), phone, mail, television, and print media. Digital communication channels include on-line (Pilarczyk, 2011). The division between traditional and digital may become however increasingly blurred. As underlined by Pilarczyk (2011), «*television is becoming interactive, the printed press has electronic issues, while advertisements have their multimedia editions and are available to countless computer users*» (p. 7).

The interaction between communication channels and promotion tools may provide a better understanding of both concepts. Table 5.1 summarizes the communication channels and promotion instruments, and their classification and interactions. The classifications shown in the table both for communication channels and for promotion tools were based on the literature review performed, and adapted from the classifications addressed by Williams & Hensel (1990), Bernewit (2001), Kotler et al (2009), Pilarczyk (2011), Kotler & Armstrong (2012), Gibson (2014), Auruskeviciene, Butkeviciene & Salciuviene (2015), and Katsanis (2015).

Table 5.1 - Communication channels, promotion instruments, and their classification and interactions

Communication			Promotion			
Channels	**Personal vs Nonpersonal**	**Traditional vs Digital**	**Tools**	**Theoretical grounding** (non-exhaustive)	**Commercial vs non-commercial**	**Push vs Pull**
Face-to-face	Personal	Traditional	Detailing (personal selling)	(Pitt & Nel, 1988; Berndt, Bui, Reiley & Urban, 1995; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kalyanaram, 2008; Dave & Saffer, 2012)	Commercial	Push
			Drug sampling	(Parsons & Abeele, 1981; Mizik & Jacobson, 2004; Fugh-Berman & Ahari, 2007; Kumar & Panigrahi, 2014; Salmasi et al, 2016)	Commercial	
			Gifts and meals	(Jastifer & Roberts, 2009; Katz, Caplan & Merz, 2010; DeJong et al (2016); King & Bearman, 2017)	Commercial	
	Both	Traditional	Continuing medical education (CME) & Event sponsoring (Conventions / Meetings / Conferences / Seminars / Lectures / Symposia)	(Pitt & Nel, 1981; Evans & Beltramini, 1986; Williams & Hensel, 1991; Noble, 1992; Davidoff, 1997; Wazana, 2000; Holmer, 2002; Relman, 2008; Steinbrook, 2008; Meffert, 2009)	Non-commercial	Both
Telephone	Personal	Traditional	Tele-detailing	(Macaluso, 2000;Berndt et al, 2007; Steinman et al, 2007; Calvagna, 2013)	Commercial	Push
Mail	Nonpersonal	Traditional	Direct-mail advertising	(Parsons & Abeele, 1981; Williams & Hensel, 1991)	Commercial	Push
Print	Nonpersonal	Traditional	Medical journal advertising	(Parsons & Abeele, 1981; Pitt & Nel, 1988; Othman, Vitry & Roughead (2010)	Commercial	Push
			Direct-to-consumer advertising (DTCA)	(Iizuka & Jin, 2005)	Commercial	Pull
Television	Nonpersonal	Traditional	Direct-to-consumer advertising (DTCA)	(Kravitz et al, 2005; Iizuka & Jin, 2005; Liang & Mackey, 2011; Liu & Gupta, 2011; Salmasi, Ming & Khan, 2016)	Commercial	Pull
On-line	Nonpersonal	Digital	Virtual (interactive) e-detailing (self-detailing)	(Bernewitz, 2001; Heutschi et al, 2003; Trucco & Amirkhanova, 2006; Alkhateeb & Doucette, 2008; Montoya, 2008)	Commercial	Pull
	Personal	Digital	Video (live) e-detailing	(Heutschi et al, 2003; Trucco & Amirkhanova, 2006; Alkhateeb & Doucette, 2008)	Commercial	Push
	Both	Digital	e-Mailing (e-mail marketing)	(Pedroso & Nakano, 2009)	Commercial	Both
	Nonpersonal	Digital	e-Continuing medical education (e-CME)	(Wutoh, Boren & Balas, 2004; Buxton, Burns & De Muth, 2012)	Non-commercial	Both
	Nonpersonal	Digital	Company websites and healthcare portals	(Shepherd, Zitners & Waters, 2000; Puschmann & Alt, 2001; Fischer, Stewart, Mehta, Wax & Lapinsky, 2003; De Leo, LeRouge, Ceriani & Niederman, 2006)	Both	Pull
	Nonpersonal	Digital	Health social networks	(Swan, 2009; Barlas, 2010; Sarasohn-Kahn, 2008; Domingo, 2010)	Both	Pull
	Nonpersonal	Digital	e-Sampling	(Puschmann & Alt, 2001; Doyle, 2007; Vecchione, 2008; Kumar & Panigrahi, 2014)	Commercial	Pull
	Nonpersonal	Digital	e-Direct-to-consumer advertising (e-DTCA) / Web 2.0	(Sarasohn-Kahn, 2008; Liang & Mackey, 2011; DeAndrea & Vendemia, 2016; Parekh, Kapupara & Shah, 2016; Southwell & Rupert, 2016)	Commercial	Pull

Source: own elaboration

5.5.Promotion tools using traditional channels

We will now analyze the promotion tools pharmaceutical manufacturers use to interact with physicians. For this analysis, we selected one of the classifications discussed before, regarding traditional and digital communication channels. Therefore, topic 5.5 will cover promotion tools using traditional communication channels, and topic 5.6 will address promotion tools using digital communication channels.

5.5.1. Detailing

As addressed previously, detailing is the most important instrument in terms of pharmaceutical promotion, in terms of investment magnitude.

5.5.1.1.Sales call and detailing: theoretical foundations

A sales call is an occasion where a PSR interacts with a prescriber (usually a physician), presenting information about a medicine. Lodish, Curtis, Ness & Simpson (1988) noted that in each sales call, or visit, several presentations (or details) can be made by the PSR. Mantrala et al (1994) explained that «*sales calls tend to be short in repetitive buying environment and therefore, sales forces actively promote only a few selected products at a time in sales cycles lasting several months*» (p. 122). Oldani (2004) explained that, in the past, detail men reps were mostly male and called mainly male doctors, and that the term detail men is linked to the nature of the sales presentation. He also described that pharmaceutical sales representatives (or sales reps) present "details" of a drug to doctors (and therefore the term "detailing"), and typically use visual aids which they keep at a book called "detail book", and then store in a bag called "detail bag". In each sales call (or visit), PSRs can present more than one detail (one detail is one product mention), up to three or four details per visit. The first product to be detailed is usually the most important for the pharmaceutical company promoting it, and typically consumes most of the time of the sales call. Montgomery & Silk (1972) noted that detailmen (PSRs) tyoically leave product samples and medical literature with the physicians, when they visit them.

Before visiting a doctor, PSRs can perform the preparation of the call, which consists of pre-call planning, a critical component of the sales call (Ahmad, 2013). Mehta (2004) suggested that effective pre-call planning should involve reviewing past call notes, review sales data, define a precise call objective, anticipate probable objections, and paly role the call.

The typical duration of a pharmaceutical sales call has been declining. Yi, Anandalingam & Sorrell (2003) found that, while in 1997 the estimated average time spent per detail pointed to

circa eight minutes, in 2001 the average had contracted to approximately four minutes (a 50% reduction, reflecting the less time physicians are spending with PSRs). John (2008) underlined that there is anecdotal evidence showing that the average time PSRs spend on a detailing visit may have dropped to less than one minute in 2004. Bernewitz (2001) proposed that the average duration of a PSR sales call is about three minutes. According to research conducted by Steinman, Harper, Chren, Landefeld & Bero (2007), typical pharmaceutical sales call lasts five minutes or less in duration. According to Cegedim (2012), the average call duration has been suffering relevant reduction from 2006 (where more than 22% of sales calls to Internists were longer than 10 minutes) to 2011 (only 9% were longer than 10 minutes).

Post-call analysis consists of the evaluation of the result of the PSR sales call, so that the next call can be more efficient. Mehta (2004) suggests that, after the call, PSRs should record the call immediately, analyze the call and prepare the follow-up call.

Molloy et al (2002) defined detailing as «*face-to-face meetings where pharmaceutical representatives (PRs) present information to physicians*» (p. 825). Other authors have proposed more complete definitions of detailing. Yi, Anandalingam & Sorrell (2003) suggested that «*in physician detailing, each sales representative targets physicians in an effort to provide accurate and latest product information, and to encourage them in prescribing the presented prescription drugs for their patients who fit the specific diagnosis criteria*» (p. 533). Steinman, Harper, Chren, Landefeld & Bero (2007) proposed a more complete definition, underlining that «*detailing involves direct visits from drug company representatives to individual doctors, during which the representative would provide information about their company's drugs*» (p. 751). Rao & Yamada (1988) explained that PSRs visit doctors, describing their portfolio of drugs, providing free samples, scientific literature, trying to combat the efforts of PSRs from competing pharmaceutical companies. Dingus, Agnihotri & Hu (2017) explained that with detailing, PSRs «*make multiple rounds of presentations informing and educating physicians in hopes that these physicians will consider their drug when writing prescriptions*» (p. 1). They also explained that pharmaceutical companies typically use detailing more heavily during the first years after a new product launch so that it can educate physicians on the new products, and that later in the drug life cicle companies tend to reduce detailing efforts and increase DTCA investments, reminding patients about the brand.

Detailing can also take place as a teleconference encounter (Steinman et al, 2007; Berndt, Danzon & Kruse, 2007). This form of detailing is known in the pharmaceutical industry as

tele-detailing, and starts with a phone call, as explained by Calvagna (2013). The PSR then calls the doctor's office and tries to schedule an appointment for a phone call. Tele-detailing - at least in its more basic form, with no digital content transfer - appears to be a rudimentary form of e-detailing. As noted by Macaluso (2000), tele-detailing is a less costly version of detailing to reach a wide range of physicians, and can be used to preserve market share, or to promote an older, mature and profitable product, but with no detail time due to newer products recently launched.

According to the Pharma Marketing Network, a «*Detail means that part of an in person, face-to-face sales call during which a sales representative, who is trained and knowledgeable with respect to the applicable product, including its label and package insert, and the use of the applicable promotional materials, makes a presentation of such product to a medical professional with prescribing authority. When used as a verb, detail means to engage in detailing activities*» (Pharma Marketing Network, 2017).

Iizuka (2004) addressed the concept of detailing intensity, which consists of the number of details (measured as an office visit with physician contact), in which a drug is detailed, in a given period (Manchanda, Rossi & Chintagunta, 2004; Liu et al, 2016).

From a sales theory point of view, detailing is a form of personal selling (Fischer & Albers, 2010), defined as the promotion of a firm's drugs to physicians, by pharmaceutical sales representatives (Mizik & Jacobson, 2004). It is however a specific type of personal selling called missionary selling, where the focus is not on the actual completion of a sales transaction and winning a sale, but rather on stimulating demand for the promoted product and on the development of goodwill, through pharmaceutical sales representatives (Weilbaker, 1990). Pharmaceutical sales representatives do not sell drugs to prescribers, but instead introduce and market their companies' products through interactions with physicians and making use of several promotion instruments such as free drug samples, gifts, free meals and sponsorships (Salmasi et al, 2016).

From a marketing theory point of view, detailing can be considered a form of relational marketing, as it builds on the development of relationships between pharmaceutical companies (through the sales representatives) with prescribers. This is consistent with Gronroos (1994) definition of relational marketing, in the sense that this relation is established between several parties, by a mutual exchange and fulfilment of promises. This type of relationship can be framed into the commitment-trust theory of relationship marketing,

proposed by Morgan & Hunt (1994). This theory is based on commitment, where «*the committed party believes the relationship is worth working on to ensure that it endures indefinitely*» (p. 23), and on trust, «*as existing when one party has confidence in an exchange partner's reliability and integrity*» (p. 23). Relationship commitment and trust are mediated by a series of variables, shown in Figure 5.2.

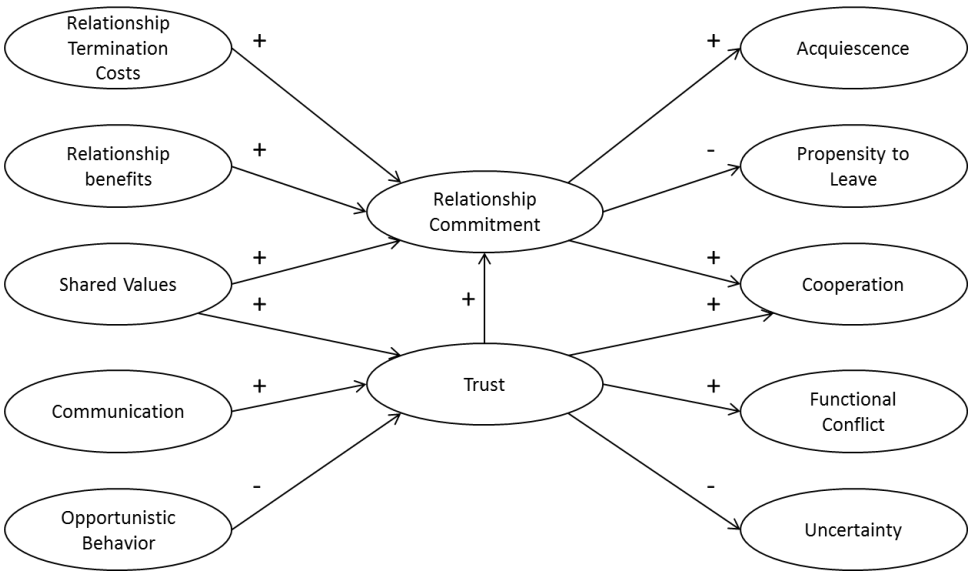


Figure 5.2 - The Commitment-trust theory of relationship marketing

Source: Morgan & Hunt (1994)

Homburg, Bornemann & Kretzer (2014) also addressed detailing in a relational scope. They addressed detailing as a long-term relational exchange, where PSRs visit physicians regularly and proactively, with the goal of influencing them to consider their company brands at the moment of selecting which drug to prescribe, reducing physicians' available market options, and as a consequence trying to commit physicians into a long-term relationship.

Wazana (2000) evidenced, in his review, that physician-industry interactions appear to affect prescribing and professional behavior, addressing the relation between detailing and physicians' prescriptions. In a more recent review, Spurling et al (2010) found that physicians that have experienced exposure to information provided directly by pharmaceutical companies display a higher prescribing frequency, or lower quality of prescription (in some of the papers no significant association was found).

Several researchers highlighted the association between detailing and prescription behavior, and its magnitude has been subject of discussion. For instance, Mizik & Jacobson (2004) research suggested that detailing has a modest impact on prescriptions. Gönül, Carter, Petrova

& Srinivasan (2001) had evidenced physicians fairly limited price sensitivity regarding detailing and samples, where these promotion instruments appear to have a mostly informative role. Wieringa & Leeflang (2013), studying several products in the Dutch market, found that the impact of marketing efforts (including detailing) is significant for only a small portion of the brands, and are moderate in size.

Conversely, other researchers found detailing to have a stronger impact on physicians' prescription behavior. For instance, Berndt, Bui, Reiley & Urban (1995) analyzed the impact of detailing and several other marketing initiatives such as DTC advertising, journal ads, and found that not only detailing has a positive impact on the number of prescriptions, but also it had the largest significant effects among the marketing initiatives.

5.5.1.2.Evidence from the literature on detailing

To the best of our knowledge, there is no explicit theory regarding detailing and its effect on prescription behavior. Yet, based on the literature review on detailing, some evidences can be extracted, summarizing the scholars' findings, interpretations and explanations, here inferred as assumptions.

Detailing is the pharmaceutical promotion tool with highest total investment magnitude, used by pharmaceutical manufacturers to interact with physicians. This evidence was underlined by Gagnon & Lexchin (2008), Yi, Anandalingamb & Sorrell (2003), and Datta & Dave (2016). These last researchers noted that more than four fifths of promotion directed to physicians is in the form of visits by PSRs (detailing)

Commonly accepted evidence about detailing suggests that the effect of detailing on brand prescriptions is on average positive, but modest (Kremer et al, 2008; Stremersch & Van Dyck, 2009; Stremersch & Lemmens, 2009). Table 5.2 below helps generate additional perspective on the type of detailing elasticities of a series of articles selected during the literature review:

Table 5.2 – Magnitude of detailing elasticities on a selected perimeter of articles

		Detailing coefficient				
Author(s)	**Drug class(es)**	**Sign (+/-)**	**Value**	**Elasticity?**	**Comment**	**Main findings (detailing related)**
Parsons & Abeele (1981)	Steroid group of prophylactic medicines for women	-	-0.148	Yes	Regression coefficient (elasticity)	Sales call (detailing) elasticity is negative when no samples or handouts are given
Mackowiak & Gagnon (1985)	Benzodiazepines and diuretics	Neutral	0	Yes	No correlation between changes in detailing expenditures, and demand (new prescriptions)	There was no correlation between changes in detailing or journal advertising expenditures and primary or selective demand (detailing elasticity is zero)
Berndt, Bui, Reiley & Urban (1996)	Antiulcer (H_2-antagonists)	+	0.553	Yes	Detailing estimate elasticity	Detailing is the most effective promotion instrument
Rizzo (1999)	Antihypertension	+	0.16	Yes	Included a dummy variable for generics, whenever a drug experienced a patent loss	Heavier detailing makes sales substantially less responsive to price
Gönül, Carter, Petrova & Srinivasan (2001)	Chronic condition among elderly	+	0.1085	Yes	Linear (-0.007 for detailing squred)	Exposing a physician to personal selling can become counterproductive beyond a certain amount of cumulative detailing
Wittink (2002)	Hypertension, asthma, arthritis, erectile dysfuntion, other	+	ROI estimates	No	Article presents ROI estimates for detailing and three other promotion instruments	Detailing evidences a positive average return on investment (ROI)
Wosinska (2002)	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	+	0.152 to 0.185	Yes	Detailing elasticities using two different models	The estimated marginal impact of detailing is significantly larger than the marginal impact of consumer advertising (on the order of five times)
Narayanan, Manchanda & Chintagunta (2003)	Antihistamines	+	0.1143 | 0.0971 | 0.0978	Yes	Allegra, Craritin and Zyrtec (respectively)	On average, physicians are most sensitive to detailing relative to other promotional activities. Detailing plays a primarily informative role in the introductory phase, but the persuasive role dominates later on
Rosenthal, Berndt, Donohue, Epstein & Frank (2003)	Anti-depress., anti-hyperlipidemics, proton pump inhibit., nasal sprays, antihistamines	Neutral	0*	Yes	Detailing elasticity estimates did not approach statistical significance (*coefficient of 0.443) for individual products	Detailing elasticities for the aggregate information by drug class were positive, but marginal (0.017 to 0.034), but not different from zero regarding individual products
Manchanda & Chintagunta (2004)	Mature product category	+	0.17	Yes	Average coefficient	There seems to be over-detailing in this product category (negative quadratic term)
Manchanda, Rossi & Chintagunta (2004)	Mature product category	+	0.038	Yes	Average coefficient	Detailing elasticity is much higher among Specialists than among non-specialists
Mizik & Jacobson (2004)	N/A	+	0.17 | 0.07 | 0.115	Yes	Estimated elasticities for Drug A, B and C (respectively)	Detailing and free drug samples have positive and statistically significant effects on the number of new prescriptions issued by a physician

		Detailing coefficient				
Author(s)	**Drug class(es)**	**Sign (+/-)**	**Value**	**Elasticity?**	**Comment**	**Main findings (detailing related)**
Narayanan, Desiraju & Chintagunta (2004)	Antihistamines	+	0.1772 | 0.095 | 0.144	Yes	Allegra, Craritin and Zyrtec (respectively). * Nerlove-Arrow exponential decay goodwill model	Detailing has a much higher impact no shares than DTCA. There is a positive interaction between detailing and DTCA (synergy)
Chintagunta & Desiraju (2005)	Antidepressants	+	0.20 | 0.28 | 0.30 0.55 | N/S | 0.59 0.17 | 0.30 | 0.23 2.43 | 2.33 | 2.32 0.22 | N/S | 0.32	Yes	Detailing elasticities for Prozac, Zoloft and Paxil (respectively) * Instead, the authors used square root for the detailing coefficient, to account for diminishing marginal returns	Detailing elasticities are different in different countries, for the same products promoted. United States, Germany, and Italy have comparable own-detailing elasticities, whereas in the U.K. and especially in France elasticities are uniformly higher. Accross market interactions were found
Narayanan, Manchanda & Chintagunta (2005)	Antihistamines	+	0.0912 | 0.0867 | 0.0795	Yes	Allegra, Craritin and Zyrtec (respectively; direct effects)	There are both indirect and direct effects of detailing. The indirect effect dominates in the introductory stages, whereas the direct effect dominates in the subsequent stages
Windmeijer, de Laat, Douven & Mot (2006)	11 therapeutic classes	+	0.3	Yes	Promotion expenditures elasticity (aggregation of detailing + advertising + direct mail)	Promotion expenditures have a positive effect on drug demand (elasticity of 0.3), and competitive promotion expenditures have a negative effect (elasticity of -0.12)
Berndt, Danzon & Kruse (2007)	Antihypertensives, antidepressants and antiepileptics	+	0.00 | '0.055 | 0.00	Yes	Elasticities for antihypertensives, antidepressants, and antiepileptics. The 1st and 3rd were non-significantly ≠ 0	Promotion of new drugs positively affects the new drug share, while promotion of old drugs negatively affects the new drug share
Venkataraman & Stremersch (2007)	Statins, gastrointestinal and coagulation, and erectile dysfunction	Neutral*	0.01 | 0.00 | -0.11	Yes	*Mean detailing elasticities for categories 1, 2 and 3 (four drugs in each category)	Detailing has a positive effect on prescriptions for 7 out of the 12 brands. Drug characteristics, such as effectiveness and side effects, moderate the response by physicians to both marketing efforts and detailing
Kalyanaram (2008)	Anti-depressants, proton pump inhibitors, and antihistamines drugs	+	0.81	Yes	Elasticity of direct-to-physician advertising (detailing + journal advertising)	The effect of direct-to-physician advertising (constituted by detailing and medical journal advertising) is significant in explaining market share
Manchanda, Xie & Youn (2008)	Chronic condition among 6% of the USA population	+	0.35 | 0.44	No	Detailing coefficients for two different territories	The effect of current detailing, detailing stock, and sampling stock is significant and positive
Vakratsas & Kolsarici (2008)	Lifestyle-related disease (anonymous)	Neutral**	0	Yes	* Instead, the authors used square root, to account for diminishing marginal returns ** Non-significant detailing coefficient	Detailing evidenced lack of significance. Relative ineffectiveness of detailing could be due to higher saturation
John (2008)	N/A	---	---	---	---	The average value of the effect of detailing is found to be 0.73 (the effect of details made in previous periods have on the current period)
Dong, Manchanda & Chintagunta (2009)	Proton pump inhibitor (gastroesophageal reflux)	+	0.115 | 0.128 | 0.131 | 0.120	Yes	Mean detailing elasticities for Nexium, Prevacid, Aciphex, Protonix (respectively)	Detailing has a positive effect on drug prescriptions. Ignoring strategic behavior underestimates the detailing elasticity
Kalyanaram (2009)	Anti-depressants, proton pump inhibitors, and antihistamines drugs	+	0.62	Yes	Elasticity of direct-to-physician promotion (detailing + journal advertising)	The coefficient of DTPA (direct-to-physician advertising) has the biggest impact on market share

		Detailing coefficient				
Author(s)	**Drug class(es)**	**Sign (+/-)**	**Value**	**Elasticity?**	**Comment**	**Main findings (detailing related)**
Narayanan & Manchanda (2009)	Erectile dysfunction	+	0.6113	Yes	Mean of the physician-specific detailing stock parameter	There is a significant amount of variation across physicians in terms of how their responsiveness to detailing varies over time
Fischer & Albers (2010)	N/A	+	0.33	Yes	Total detailing elasticity (short + long term)	On average, detailing is the most potent driver of primary demand among the three communication-mix elements analyzed
Fischer, Leeflang & Verhoef (2010)	Calcium channel blockers and ACE inhibitors (antihypertensives)	+	0.099 | 0.507	Yes	Elasticities for stock of own marketing vs Time-to-peak-sales and Height-of-peak-sales, respectively | * Quarterly discount rate	Marketing (promotion) expenditures increase the level of peak sales, while they decrease the time-to-peak-sales
Gönül & Carter (2010)	6 classes	+	0.509	No	Standardized regression coefficient; *Used cumulative discounted detailing	Both e-detailing and traditional (face-to-face) detailing have positive effects on the number of new prescription sales, but detailing effect is dominant
Leeflang & Wieringa (2010)	11 classes	+	0.014	Yes	Detailing average coefficient for all drug brands. *Used detailing discount rate	Detailing is effective for more brands than the other instruments. However, the effects sizes are modest and occur infrequently
Montoya, Netzer & Jedidi (2010)	Medical condition in postmenopausal women	+	0.654	Yes	Total detailing elasticity (short + long term)	Detailing is most effective as an acquisition tool, whereas sampling is most effective as a retention tool
Nair, Manchanda & Bhatia (2010)	Serious chronic disease that affects 1/4 of the US adult population	+	0.825	No	OLS regressions coefficient (physician prescriptions on opinion leader's prescriptions)	Estimate of the detailing coefficient is large and strongly statistically significant. This social multiplier of detailing is economically significant
Dong, Chintagunta & Manchanda (2011)	Proton Pump Inhibitor (PPI) and antidepressants (AD)	+	0.13 to 0.28 | 0.09 to 0.20	Yes	Range of own detailing elasticities for PPI and AD drugs	A firm's detailing level in a category appears to be influenced by how much that physician was detailed by that and the rival firms in the previous time period; and by the firm's detailing in other categories (spillover effect)
Ching & Ishihara (2012)	ACE inhibitor with diuretic (antihypertensives)	+	0.183	No	Detailing coefficient for the partner cumulative detailing efforts	The informative role of detailing is mainly responsible for the diffusion patterns, whereas the persuasive role plays a crucial role in determining the demand for brands that co-market the same chemical
Dave & Saffer (2012)	Analgesics / musculoskeletal, anti-lipidemics, gastrointestinal acid reducers, insomnia aids	+	0.51	Yes	Detailing elasticity	Ddetailing is more effective at raising own-sales than is DTCA
Wieringa & Leeflang (2013)	Ulcers, hypertension, cholesterol, depression, and asthma	+	0.001	Yes	Mean of brand level elasticity coefficient for marketing flow	Several models can be applied to study the effects of promotion expenditures on drug sales
Ruiz-Conde, Wieringa & Leeflang (2014)	Rhinitis, arthritis, asthma	+	0.005	Yes	Direct-to-physician (detailing + medical journal advertising; physician meetings; DTCA) coefficient, for the informative role	During the first 12 months after the introduction of a new drug, managers should concentrate their efforts mainly on direct-to-physician activities, that allow pharmaceutical companies to increase the trial rate

		Detailing coefficient				
Author(s)	Drug class(es)	Sign (+/-)	Value	Elasticity?	Comment	Main findings (detailing related)
Datta & Dave (2016)	Antivirals	+	0.06	Yes	Estimated elasticity	Detailing has a significant and positive effect on the number of new scripts written for the detailed drug
Kappe & Stremersch (2016)	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	+	0.042	Yes	Short + long-term detailing elasticity (controlling for information content)	In the first 6 months following generic entry, it is more effective for incumbent brands to detail on drug contraindications and indications
Liu, Gupta, Venkataraman & Liu (2016)	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	+	0.533, 0.225, 0.218	Yes	Detailing stock effects for Crestor, Zocor and Lipitor (respectively)	For all three brands, the estimates of detailing stock effects are positive and significant, confirming results from previous studies
Mukherji, Jaimakiraman, Dutta & Rajiv (2016)	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	+	0.000112	No	* Nerlove-Arrow exponential decay goodwill model for detailing carryover + square root for detailing wearout	The detailing parameter is positive and significant
Chung, Kim & Park (2017)	Chronic pathology	+	0.092 to 0.251	Yes	Detailing elasticities were calculated for each of the six doctor specialties. Prescriptions as sum of all brands	Specialist physicians exhibit a greater long-term effect but only modest short-term responsiveness to detailing, when compared against generalist physicians
Kappe, Venkataraman & Stremersch (2017)	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	+	1.73, 0.35, 0.80, 0.82	Yes	Elasticities for Crestor, Lipitor, Pravachol, and Zocor	A detailing decrease for market-leader (Lipitor) triggers competitors to often decrease their detailing as well, while a decrease in detailing for Pravachol triggers competitors more often to increase their detailing
Liu, Liu & Chintagunta (2017)	HIV / AIDS	+	0.002 to 0.189	Yes	Elasticities consistent with previous findings from other researchers	Detailing for one drug can increase demand for other drugs that are often combined with the focal drug. Such spillover effects could lead to free riding by the drugs benefitting from the spillover
Shapiro (2018)	Antipsychotics	+	0.3	No	Each detailing visit causes roughly 0.12 prescriptions in the month of the visit and 0.3 over time	The effect of detailing on off-label prescriptions is small in both absolute and relative terms

Source: own elaboration

As expressed above in table 5.2, the literature on pharmaceutical marketing suggests that detailing has a significant and positive impact on physicians' prescribing behavior, but several studies point to a neutral impact, or even a negative one. According to Venkataraman & Stremersch (2007), «*one reason why this may happen is that physicians' response to marketing efforts may actually depend upon drug characteristics, such as a drug's effectiveness and side effects*» (p. 1699). By studying the effects of detailing, meetings, patients' drug requests, drug samples, and drug characteristics (effectiveness and side effects) on drug sales, they found that «*drug characteristics, such as effectiveness and side effects, moderate the response by physicians to both marketing efforts and detailing, both in their prescription and their sampling behavior*» (p. 1699). As an implication for the pharmaceutical industry practice, Venkataraman & Stremersch (2007) underlined that detailing activities will more likely produce positive impacts on physicians' prescribing behavior if these activities are supporting drugs that are effective or that have many side effects.

Neutral elasticities have been found on detailing impact on prescription behavior. Mackowiak & Gagnon (1985) studied the effect of expenditures in detailing and medical journal advertising, on the number of new prescriptions of several drugs in the benzodiazepines and diuretics class. Using ARIMA time series analysis, they found no correlation between changes in detailing and journal advertising expenditures, and demand (new prescriptions), suggesting that these investments had, for the data series studied, an elasticity of zero. Rosenthal, Berndt, Donohue, Epstein & Frank (2003) studied five therapeutic classes of drugs, analyzing the impact of DTCA, detailing, and other variables (order of entry, drug price, drug age (measured as time remaining with patent)) on the number of prescriptions (sales), and found that detailing had a very small elasticity (0,017 to 0,034), regarding information aggregated by drug class. However, when they analyzed the drug brands separately, detailing elasticities were not statistically significant, and therefore not different from zero.

Vakratsas & Kolsarici (2008) studied the relation between new prescriptions and detailing, medical journal advertising, and DTCA using data from a non-US country, aggregating data from a drug class, and found that only medical journal advertising and DTCA produced significant elasticities. They suggested that perhaps the detailing non-significant coefficients were explained either by the fact that they were using class-aggregation, or due to the possible detailing saturation in that drug class.

Some research produced even negative detailing elasticities. For instance, Parsons & Abeele (1981), using data from Belgium regarding steroid group of prophylactic medicines for women, studied the effect of detailing and other promotion instruments such as mailing, samples, and handouts, on drug sales, and found that detailing had a negative elasticity (-0,148) when drug samples and handouts are not give to doctors. They also found that detailing only had a positive (however very low) positive effect in interactions with samples (0,030) and handouts (0,029) when combined separately, but a negative effect when including both drug samples and handouts (-0,005). Venkataraman & Stremersch (2007) also found that, for some of the products included in their data set, some products evidence detailing negative elasticities, suggesting that effects of marketing efforts on prescription behavior vary by drug brand.

However, despite the few cases where detailing elasticities are neutral or negative, the majority of the previous research points to a positive elasticity, as found by Kremer, Bijmolt, Leeflang & Wieringa (2008), reaching an average elasticity of 0,326.

Despite the apparent modest effect on prescription behavior, detailing appears to be the promotion instrument that generates a higher effect on prescription behavior, which has been covered by several researchers. Pitt & Nel (1988) were one of the first ones and found that doctors recognize detailing (sales calls by pharmaceutical sales representatives) as the most powerful and significant promotion tool in terms of its ability to influence prescription. Berndt, Bui, Reiley & Urban (1995) found that not only detailing has a positive impact on the number of prescriptions, but also it had the largest significant effects among the marketing initiatives. Wosinska (2002), when analyzing the impact of detailing and DTCA on the number of new prescriptions, concluded that «*the estimated marginal impact of detailing is significantly larger than the marginal impact of consumer advertising (on the order of five times)*» (p. 2). Narayanan et al (2003) found that detailing is relatively more impactful than other promotion activities, in terms of drugs prescriptions. Narayanan, Desiraju & Chintagunta (2004) found that detailing has a much higher impact on shares than does DTC. Narayanan, Manchanda & Chintagunta (2005), found that detailing elasticities have a higher magnitude than DTC and other marketing expenses Kalyanaram (2008) concluded that direct-to-physician (DTP) advertising has a much higher elasticity than DTC advertising. In another similar analysis, Kalyanaram (2009) concluded again that DTP advertising has a much higher elasticity than DTC advertising. Dave & Saffer (2012) also found evidence of a much higher magnitude of the detailing elasticity than the DTC advertising elasticity. Mukherji,

Jaimakiraman, Dutta & Rajiv (2017) also highlighted that detailing is the most impactful tool, playing a larger role than DTCA in individual drug choice. The magnitude of the effect of detailing and other promotion instruments on prescription behavior will be more deeply analyzed in a specific topic, later in this thesis. This evidence will be further analyzed in topic 5.8.5. Comparative effectiveness of the promotion tools.

Detailing appears to reduce price elasticity of drugs. Gönül et al (2001), when studying a drug and diagnosis data, personal selling data, and retail price data, found that physicians are characterized by fairly limited price sensitivity, since, globally, physicians' price sensitivity appears to come second to considerations about drug efficacy and patients' conditions. This conclusion is consistent with results obtained by Rizzo (1999), who studied the effect of product promotion through detailing to antihypertensive grugs, concluding that it inhibits price competition, leads to higher prices, lowering price elasticities of demand (price elasticities using a model with no detailing were substantially higher than price elasticities using detailing and detailing stock). Windmeijer et al (2006), when studying several products from different therapeutic classes using data from The Netherlands, also concluded that promotion expenditures (where detailing accounted for 63% of the total expenditures) adversely affect the own-price elasticity of drugs, reducing price elasticities to practically zero, shifting the demand curve outwards. Narayanan et al (2004) found a somewhat converse evidence applicable in the scope of high levels of detailing. When studying the interaction between price and detailing, they suggested that that, «*because a higher price adversely affects demand, the negative interaction implies that at higher levels of detailing, the demand is even more sensitive to higher prices*» (p. 103).

Detailing effect on prescription behavior seems to evidence diminishing marginal returns. This was addressed by Berndt et al (1995), where they found that marketing initiatives (including detailing) appear to display overall decreasing returns to scale. Gönül et al (2001) highlighted that physician prescription probability curve showed an inflection after a detailing threshold (detailing squared showed a negative signal). Nevertheless, there seems to be room to increase detailing as some pharmaceutical companies may be operating on the increasing part of the curve. Manchanda & Chintagunta (2004) also found evidences of diminishing returns of the impact of detailing on the number of prescriptions (for two thirds of the physicians in their panel), somewhat more frequent among specialists. They argue that after a certain point, detailing may provoke a negative effect on prescriptions, where excessive detailing may result in a backlash, given physicians' opportunity cost of time, concluding that

overdetailing may be an issue of worry to pharmaceutical companies, because it translates into "wasted" marketing expenditures. Dong, Manchanda & Chintagunta (2009). When computing non-aggregated (nominative) information from a physician panel, also found this behavior regarding detailing impact on physicians' prescription behavior, noting that every physician has his or her own response curve to detailing activities. They exemplified this evidence in figure 5.3. X axis represents the number of details (visits) per quarter, and Y axis the number of prescriptions.

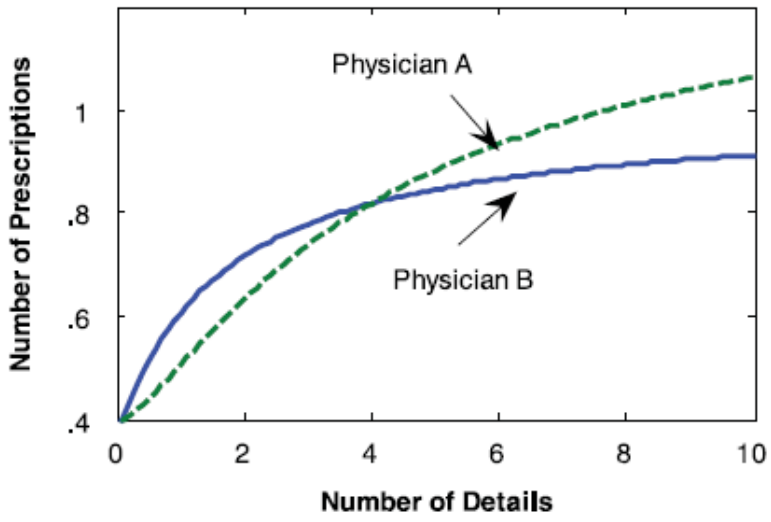


Figure 5.3 – Response curves for two individual physicians

Source: Dong, Manchanda & Chintagunta (2009)

John (2008) found in his research that detailing has a concave sales-response curve, stating that «*a plateauing effect with increasing detailing frequency can lead to not only wasting resources but also decreasing sales to irritated customers*» (p. 1750). Yi, Anandalingam & Sorrell (2003) had already addressed this issue, noting that detailing activity typically reaches a plateau, after which its effectiveness is questionable. Liu et al (2016) also noted, in their research of detailing under counterfactual detailing restriction policies, that pharmaceutical companies tend to «*direct less detailing to a physician if they already have a high detailing stock at that physician*», and that «*because of the diminishing marginal returns to detailing, it is less profitable for a firm to detail a physician if there is already a high level of detailing stock at the physician*» (p. 14). Figure 5.4 evidences the typical concave-shaped response curve, where Xi represents the number of details to a i doctor, Yi represents the average number of prescriptions of a i doctor, and Ki represents the plateau prescription amount for Yi, as Xi tends to infinite.

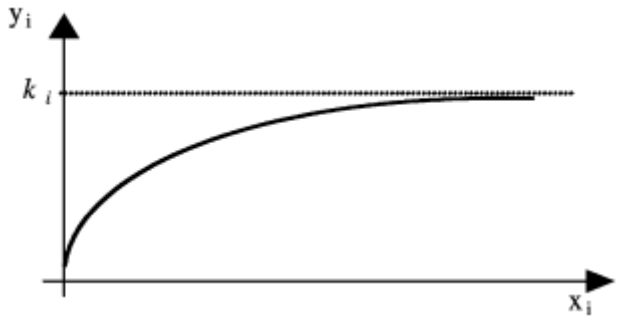


Figure 5.4 - Concave-shaped promotional response curve

Source: Yi, Anandalingam & Sorrell (2003)

Detailing efforts appear to have a higher effect on prescriptions at the initial stages of the product life cycle. Narayanan et al (2003) concluded that detailing plays a primarily informative role in the 9-18 months post drug introduction – or the introductory phase –, whereas the persuasive role dominates later on for the growth, maturity and decline phases. They suggest that pharmaceutical companies should concentrate their detailing effort more heavily at the introduction phase, followed by lower levels of detailing in later stages of the product life cycle. Two years later, the same authors (Narayanan et al, 2005) demonstrated that detailing seems to impact drug prescriptions in a stronger way in the early stages of the product life, showing that not only detailing effect on prescriptions is larger in the early stages of the product life cycle, but also that detailing plays a more informative (indirect) role in these stages, while in later stages of the product life cycle detailing plays a more persuasive (direct) role. Manchanda, Rossi & Chintagunta (2004) suggested that detailing may be more important, in terms of its effect on drug sales, regarding drugs in the growth phase of the product life cycle (comparing to drugs in the near end of their patent life). Dave (2013) highlighted that pharmaceutical promotion has both informative and persuasive elements. Despite the effect may be stronger in the initial stages of the life cycle, detailing appears to impact prescriptions in all stages of the product life cycle, as noted by Manchanda & Honka (2005) in their review. They explain that in addition to provide a "reminder effect", constant interaction between the pharmaceutical sales representatives and the physicians may build a stock of goodwill based on social and cultural factors, which can be translated into a positive prescription behavior by the prescriber.

Detailing is known to have significant carryover effects, as noted by Liu et al (2016). Zoltners, Sinha & Lorimer (2004) had already noted that the impact of sales force effort on sales is not always immediate, since sales force effort affects sales not only in the current

period, but also in future periods. They explained that carry-over can be explained because of habit, because of long-term contracts (which in the pharmaceutical industry is linked to formularies, which impose a specific drugs and brands perimeter for physicians), or because of high switching costs. Figure 5.5 illustrates a Zoltners, Sinha & Lorimer (2004) example of carry-over.

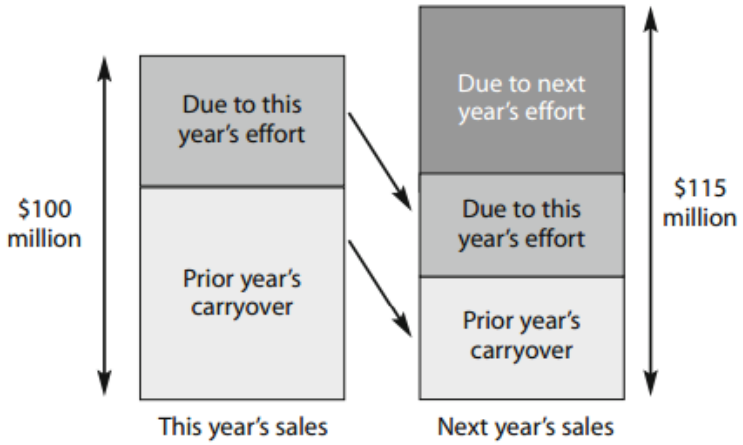


Figure 5.5 - Illustration of carry-over

Source: Zoltners, Sinha & Lorimer (2004)

John (2008) defined carry over as the impact of the details made in previous periods on those made in the current period, meaning that current detailing investments appear to affect prescribers' goodwill in future periods too. Liu, Liu & Chintagunta (2017) explained that detailing carryover is created via goodwill accumulation «*from one period to another even for drugs that have been on the market for a while*» (p. 3), also noting that detailing activities made today may influence physicians' prescription behavior (decisions) in the future. Detailing carryover was addressed by Narayanan et al (2004), when analyzing the effect of marketing investments in the current period and in multi periods. By allowing their model to incorporate the impact of current detailing activity not only in the current period but also in future periods, for example in the case of antihistamines class, the carry over reached 86% for detailing and 75% for DTC advertising, with detailing return of investment ranging from 7,6 to 9,1, and from 2,7 to 3,8, respectively. John (2008), when studying the carry over effect at the customer level in a relatively new therapeutic area, obtained a carryover effect for each responsive physician of 0,73 on average, or, 73% of the current effect of detailing was originated in previous quarters. Montoya, Netzer & Jedidi (2010) demonstrated the different effects of detailing on the number of prescriptions, on the short and long-term. They

suggested that the duration of the effectiveness of one detail may reach 10 months (5 months for sampling), after which the increase in the number of prescriptions is less than 1% (short-term elasticities appear lower than long-term elasticities). This effect can be seen below in figure 5.6.

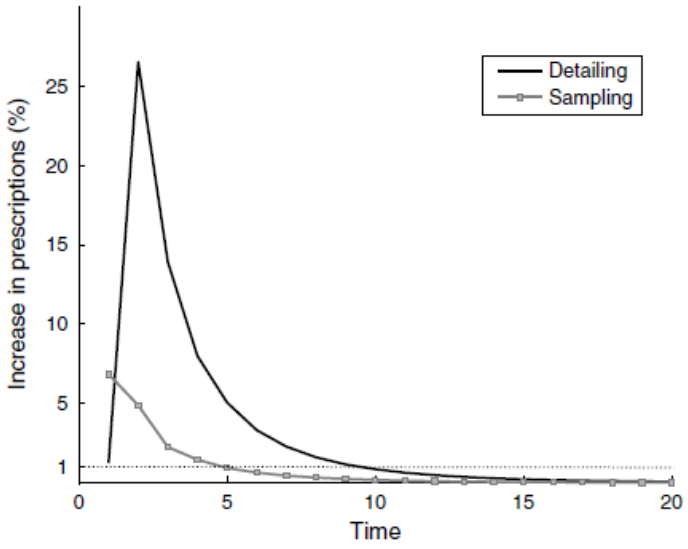


Figure 5.6 – Duration of the effect of detailing and sampling

Source: Montoya, Netzer & Jedidi (2010)

Detailing stock is, as noted by Ching & Ishihara (2012), the cumulative effects of detailing over a period of time. Rizzo (1999) explained why detailing builds a stock, pointing two reasons: first, given that patients need a prescription from a physician, and that the latter is most likely unware of all indications and side effects of all competing drugs in the market, drug promotional activities directed at physicians in one period (influencing them to initiate the prescribing of a specific drug) will probably have long-lasting effects. Second, since most drugs treat chronic conditions, when a patient starts taking a specific drug with a specific dosage that keeps him or her medical condition stable, the physician will not likely switch the drug for a competing one, except important side effects arise. Therefore, as underlined by Rizzo (1999), «*if promotional activities can encourage patients to start using a product in one period, sales will likely extend into the future*» (p. 96).

Detailing stock has however a depreciation rate (or forgetting rate), which accounts for the fact that physicians may forget drug attributes over time, as underlined by Ching & Ishihara (2012), therefore evidencing the importance of «*reminding physicians of the most updated information about drugs*» (p. 2). This concept is known as monthly depreciation rate (Rizzo,

1999), detailing stock discount (Gönül et al, 2001), detailing stock decay (Narayanan, Manchanda & Chintagunta, 2003), and wearout (Mukherji, Jaimakiraman, Dutta & Rajiv, 2017; Wosinka, 2012; Manchanda & Chintagunta, 2004). Gönül et al (2001) explained that discounting «*enables us to include effects such as memory decay and the fading impact of past detailing and samples with time*» (p. 85), and Windmeijer, de Laat, Douven & Mot (2006) noted that the «*stock of promotion expenditures depreciates faster for new products*» (p. 21). Gönül & Carter (2010) also noted that doctors are «*most likely to be influenced by more recent sales calls than by those in the past*» (p. 103), and therefore «*the discounting formula accounts for both memory decay and the receding impact of past promotion efforts with time*» (p. 103). Previous research used detailing stock depreciation montlhly rates of 1% (Gönül et al, 2001), 4,1% (Ching & Ishihara, 2012), 4,2% (Berndt, Bui, Reiley & Urban, 1996), 4,6% (Windmeijer, de Laat, Douven & Mot, 2006), 5,8% (Manchanda, Xie & Youn, 2008), 14% (Narayanan, Desiraju & Chintagunta, 2004; Liu et al, 2016), 20% (Datta & Dave, 2016), and 30% (Narayanan, Manchanda & Chintagunta, 2005), to name a few authors.

In the case of the research conducted by Berndt, Bui, Reiley & Urban, 1996), the monthly depreciation rate of 4,2% meant that the yearly detailing stock depreciation reached about 40 percent. They explained that «*relative detailing efforts have a long-lived rivalrous impact that depreciates at about 40 percent per year*» (p. 26). Narayanan, Manchanda & Chintagunta (2003) noted that, by using a carryover coefficient of 70% (representing a discount of 30% per month), the effect of expenditure on a marketing activity is diminished by approximately 90% in 6 months (1 – 0,7^6 = 88,2%). Rizzo (1999) had proposed the use of a detailing stock discount rate (consumer price index), and Leeflang & Wieringa (2010), analyzing data from the Netherlands, also incorporated a discount rate for detailing stock.

Detailing effect on prescriptions appears to be more on drug shares, rather than on drug category volume. Narayanan et al (2004) found that detailing has a significantly higher impact on drug shares than DTC, whereas DTC has a significant impact on category volume only), and Datta & Dave (2016) suggest that direct to physician promotion (including detailing) cannot induce untreated consumers to visit the physician, and therefore its impact on class-level demand is inherently limited.

Detailing may have different effects on prescription, depending on the type of prescription payer. The possession of prescription drug insurance may impact detailing elasticities, as evidenced by Gönül et al (2001), where physicians mostly seeing patients with private health insurance seemed to be more prone to be influenced by detailing, versus other patients mostly

seeing Medicare (federal) insurance. Similar conclusions were driven from Datta & Dave (2016) research, where detailing effects on prescription were higher for physicians whose patients were privately insured, suggesting that, if physicians are aware of the cost to the patients, then they may likely be more prone to prescribe a more expensive branded drug when the patients have drug insurance.

Detailing elasticities depend on the therapeutic or disease classes. Table 5.2 evidenced the analysis of 44 articles studying detailing impact on prescription behavior, and showed a diverse number of elasticities, considering several drug classes or categories. Kremer, Bijmolt, Leeflang & Wieringa (2008) in their review, found that different disease categories evidenced different impacts on physicians' prescriptions, on the presence of promotional instruments. The predicted elasticities of direct-to-consumer advertising, detailing, advertising (medical journal advertising), and other direct-to-physician promotion instruments are shown below in figure 5.7:

Disease category	Promotional Instrument							
	DTC		Detailing (DTP)		Advertising (DTP)		Other DTP	
Inflammations	.209	(10)[a]	.549	(16)	.065	(22)	.121	(57)
Heart and vascular diseases	.256	(36)	.392	(33)	.295	(13)	.424	(22)
Hypersensitivity	.077	(26)	.244	(35)	.305	(3)	.192	(12)
Skin diseases	−.297	(5)	1.069	(40)	.457	(14)	.731	(6)
Neurology and psychology	−.206	(6)	.317	(42)	–		.220	(47)
Other	.312	(71)	.331	(86)	.328	(44)	.256	(135)
Average	.073		.326		.123		.062	

[a] Number of elasticities.

Figure 5.7 – Predicted elasticities for combinations of promotional instruments and disease categories

Source: Kremer, Bijmolt, Leeflang & Wieringa (2008)

Kremer, Bijmolt, Leeflang & Wieringa (2008) found that direct-to-physician (DTP) instruments (mainly detailing) were most effective than DTCA, and that detailing elasticity is higher in skin diseases (1,069) and inflammations (0,549) categories. Stremersch & Van Dyck (2009) also suggested that detailing effect can be different by with physician and drug.

Detailing may have a different impact on different medical specialties. Chung, Kim & Park (2017) studied data gathered from a panel of close to 10 thousand physicians in India and found that specialist physicians tend to reveal a higher long-term effect of detailing, revealing however modest short-term responsiveness to this promotion instrument. Conversely, they

found that generalists are more likely to be more responsive to detailing in the short term, with however a lower lasting effect in time.

Detailing may be linked to nonrational prescription behavior. Wazana (2000) noted in his review that most studies addressed some negative outcomes associated with the interaction between the pharmaceutical industry and physicians. These included a series of effects, including a negative impact on physicians' ability to identify wrong claims about medication; effects on «*awareness, preference, and rapid prescription of a new drug*» (p. 378); effects on physicians' behavior, by «*making formulary requests for medications that rarely held important advantages over existing ones*» (p. 378); also included «*nonrational prescribing behavior; increasing prescription rate; prescribing fewer generic but more expensive, newer medications at no demonstrated advantage*» (p. 378). Some of these evidences were explicated by Haayer (1982), in their research on the impact of different sources of drug information on general practitioners prescribing rationality, where they found that physicians who relied on pharmaceutical representatives evidenced a lower likelihood of a rational prescribing. Brax et al (2017) developed a literature review of the impact of pharmaceutical manufacturers' interactions on physician prescription behavior, and found evidence, on 15 of the 19 selected articles, an association between promotion interactions and a inappropriate increase in prescribing rates, lower quality in the prescription activity, and / or higher prescription costs.

Detailing promotional instrument effect may be leveraged by selecting the right key opinion leaders to impact. Nair, Manchanda & Bhatia (2010) demonstrated a social multiplier of detailing to opinion leaders, where targeting these specialists may generate a 5%-35% increase on detailing return on investment. Key opinion leaders are «*influential doctors engaged by industry to advise on marketing and help boost sales of new medicines (…) in hospitals and universities (…)*» (Moynihan, 2008, p. 1402), and which are paid fees to influence their peers on behalf of pharmaceutical companies. Jacob (2018) defined KOLs (or Thought Leaders) as «*those clinicians who are considered as experts in their respective fields by their peers by virtue of their subject expertise, experience, research, publications, speaking and overall influence*» (p. 6). Tan (2003) noted that key opinion leaders assist the complex research and marketing activities, and typically are doctors who published peer-reviewed articles, have an academic title, and benefit from credibility among colleagues. Key opinion leaders are in many occasions instructors to their colleagues, speakers at meetings, and senior editors of textbooks (Meffert, 2009). These leaders can absorb almost one fourth of the

pharmaceutical manufacturers' new product commercialization budget (Nair, Manchanda & Bhatia, 2010). Meffert (2009) noted that key opinion leaders can significantly influence prescribing habits and increase relationships with the pharmaceutical industry, based on their positions of honor and respect among their peers.

Gifts and meals associated with detailing may impact prescription behavior. Katz, Caplan & Merz (2010) suggest that even small gifts called reminder gifts (pens and notepads) and meals may influence doctors' drug choice. They explored the effect of gifts on behavior, in the sense that gift recipients may feel the need to reciprocate, even if he or she is not aware or conscious that this may influence their behavior. According to Cialdini (1984), «*by virtue of the reciprocity rule, then, we are obligated to the future repayment of favors, gifts, invitations, and the like*» (p. 13). DeJong et al (2016) studied the impact of pharmaceutical industry-sponsored meals and physician prescribing patterns for Medicare beneficiaries, finding an association between the receipt of those meals (with an average value of less than US$20) and an «*increased rate of prescribing the promoted brand-name medication relative to alternatives within the drug class*» (p. 1121). King & Bearman (2017) studied the association between prescription of psychotropic medications and gifts receiving, finding that the uptake of new expensive medications was significantly lower in US states with marketing regulation, when compared to states allowing unrestricted pharmaceutical marketing. In states that were banning all gifts, the drop in market shares ranged from 39% to 83%. They suggested that gift bans and gift restrictions were much more powerful in terms of prescription reduction, than disclosure policies.

Recipients of the detailing activities (prescribers) do not consider themselves as influenced as their colleagues. Research conducted by Steinman, Shlipak & McPhee (2001) pointed to more than 60% of the physicians stating that pharmaceutical industry promotions and contacts did not have influence on their own prescribing, while only 16% believed other physicians were unaffected. Sah & Fugh-Berman (2013), in their paper on physicians influence by the pharmaceutical industry, reinforced this evidence, by underlining that «*Physicians' mistaken belief that they are immune to marketing aligns with research showing that people rationalize and believe what they want to believe. For example, studies consistently show that promotion increases the prescription of targeted drugs, yet research also finds that physicians believe their own prescribing behavior is unaffected by industry influence, although they concede that other physicians are susceptible to such influence*» (p. 666). Riese et al (2015) also found similar evidence among trainees, as they were more likely to believe that pharmaceutical

industry interactions have no impact on their own prescribing behavior, versus the prescribing behavior of other physicians. This pattern is also underlined by Salmasi et al (2016) in their review, as a certain perception of own immunity against pharmaceutical companies' promotion initiatives.

Detailing effectiveness can be optimized, in order to reach higher levels of sales force efficiency. Several authors have researcher detailing optimization. Yi, Anandalingam & Sorrell (2003), using data mining in neural networks, and also non-linear programming, studied and optimized sales response functions for several physician segments (deciles), reaching a higher level of profits when comparing the base scenario. The optimized physician detailing planning allowed an increased profit of 10%. Manchanda, Rossi & Chintagunta (2004) referred, in their paper addressing response modeling with nonrandom marketing-mix variables, that «*high-volume physicians are detailed to a greater extent than low-volume physicians without regard to responsiveness to detailing*» (p. 467), and that high-volume physicians, but unresponsive to incremental detailing efforts, are detailed the most. The results obtained were an optimization of the number of details per physician, inducing a higher number of prescriptions.

Several years later, Montoya, Netzer & Jedidi (2010), in the scope of a new drug introduction by a major pharmaceutical company, and studying the short and long-term effects of pharmaceutical promotion activities in a sample of 300 physicians, found that the company could significantly increase its profits by optimizing the number of calls to physicians, even reducing the overall spending with detailing activities. The detailing dynamic allocation to physicians allowed a 61,9% increase in prescription versus the base scenario, representing incremental USD$412 per month, per physician, decreasing spending with detailing in 20%. Optimizing the number of calls may however be challenging for most companies. A first reason is that marketing resource allocation decisions are complex (Montoya, Netzer & Jedidi, 2010). A second reason is that, as noted by Manchanda, Rossi & Chintagunta (2004), these models and skills are not generally accessible since the have only recently been proposed in academic literature. And a third reason is that, except for the USA and New Zealand, physicians-level prescription data is not available for pharmaceutical companies.

Venkataraman & Stremersch (2007) demonstrated, in their research, that drug characteristics can moderate the effect of detailing in prescription behavior. As an implication for the pharmaceutical industry practice, Venkataraman & Stremersch (2007) underlined that detailing activities will more likely produce positive impacts on physicians' prescribing

behavior if this activities are supporting drugs that are effective or that have many side effects. Kappe & Stremersch (2016) also demonstrated that detailing effectiveness can be optimized. They studied the effects of information content in sales calls promoting statins, in the scope of entry of competing brands and generics, and found that in the first semester after generic entry, branded incumbent companies should detail doctors stressing drug contraindications and indications, compared to the period after the first semester, to positively differentiate, as they explained, the brand from generics. They also found that, in the scope of a competitive brand entry (not generic), and in the first semester following this new entry, it will be less effective for branded incumbent companies to detail doctors stressing drug indications and costs, considering the added competitive pressure.

There are physician profiles and situations that increment the likelihood of a more frequent engagement of physicians with PSRs. Primary care doctors are more likely to see PSRs, as well as high volume prescribers, and doctors working at small and urban practices are more likely to see PSRs too, as addressed by Alkhateeb, Khanfar, & Clauson (2009). They also underlined that doctors who practice in organizations that do not pose restrictive policies for pharmaceutical detailing are more likely to receive PSRs visits, as well as doctors who do not have academic affiliations. High prescribing physicians have a higher propensity to receive PSRs in detailing activities (Gönül & Carter, 2012).

Detailing effectiveness can be attenuated by a form of detailing called academic detailing. Some countries such as the US (states of Pennsylvania, Columbia, Massachusetts), Canada and Australia (Fischer & Avorn, 2012) have tested a different form of detailing, called academic detailing programs (Grande, 2009). These programs are also known as educational outreach visits, university-based educational detailing, or educational visiting (O'Brien et al, 2007). As proposed by Fischer & Avorn (2012), academic detailing «*takes the effective outreach strategies of pharmaceutical marketing and applies them to the service of promoting unbiased, noncommercial reviews of the totality of the existing evidence on a particular clinical topic, along with practice recommendations based on that evidence*» (p. 2207) using trained nurses, pharmacists or physicians to meet with prescribers at their own offices. In these publicly-funded programs, the goal is not to regulate, but rather to substitute pharmaceutical detailing, trying to counter its influence, as noted by Grande (2009). According to the researcher, these programs – using the same sales tactics applied by the pharmaceutical industry to impact physicians' prescribing behavior and attitudes, but using evidence based guidelines – but the programs alone may not however be a «*complete answer*

to the larger challenge of moderating the influence of pharmaceutical gifts on physicians» (p. 81). O'Brien et al (2007) reviewed literature on academic detailing and found that it can produce moderated but potentially important effects in improving health professional practice, reducing the difference in compliance against desired medical practice.

Detailing efforts performed by competitor drug brands affect own brand number of prescriptions. These detailing efforts are called, in the pharmaceutical literature, as competitive detailing, and will be covered further in this thesis. We present, however, two articles addressing competitive detailing impact. The first is the research performed by Dong, Manchanda & Chintagunta (2009). They found that the higher the intensity of competitors detailing, the lower the sales of the own brand and that the effects are different for different competitor brands. Finally, they found that the competitive effects were the strongest in the zero to two details range. Liu et al (2016) found that detailing leaders will suffer the highest reduction in share of voice and market share (against other competitors and generics, when available).

Direct-to-physician promotion – from which detailing is the most important component – can have an impact on companies' stock returns, when there are unexpected schocks (increase in direct-to-physician promotion) investors were not counting on, as explained by Osinga, Leeflang, Srinivasan & Wieringa (2011). Dingus (2014) studied the impact of detailing investments and stock returns of six of the top pharmaceutical manufacturers in the USA, and found that «*the growth rate of detailing does have a positive, significant impact on firm valuation*» (p. 20). Dingus, Agnihotri & Hu (2017) studied the effect of detailing and DTCA investments in the top 6 pharmaceutical companies in the US, with data from the period of 1995 to 2012, and found that both promotion instruments did have a significant and positive effect on the firms' value (measured as Tobin's Q and stock return).

Detailing can have spillover effects. Dong, Chintagunta & Manchanda (2011) studied the effect of detailing on multi-category physician prescription behavior, and found that a company detailing level in one drug category may be influenced by the company detailing level in other categories, which constitutes a spillover effect of detailing, that is, the reach and impact of detailing may not be circumscribed to the drug category being impacted. They suggest managers to incorporate these findings into the doctors' segmentation to achieve higher levels of responsiveness to the company detailing efforts, and to its profitability. More recently, Liu, Liu & Chintagunta (2017) studied detailing spillovers in the scope of combination therapies, that is, «*simultaneous administration of two or more medications to*

treat a single disease» (p. 1), or by other words situations where there is a bundle of products typically from different companies. They studied several product bundles and ran counterfactual simulations to test several scenarios in HIV / AIDS drug class, and found both detailing spillovers and free riding effects. They concluded that the detailing efforts a company makes for its brand (focal) may not only benefit its prescription volume, but also benefit the prescription volume of drugs used in combination with this focal brand. In these situations, Liu, Liu & Chintagunta (2017) noted that those brands from other companies benefit from the focal brand promotion efforts, which they call a free ride from the detailing spillover.

5.5.1.3.Competitive detailing

The concept of competitive detailing was addressed by Liu et al (2016) in their article covering an empirical model of drug detailing, studying dynamic competition and policy implications. Competitive detailing can be interpreted as the detailing activity dynamics of the competitors in a specific drug class. By other words, it translates the dynamic and reactions of competitors regarding their detailing investments decisions and is directly related to the concept of share of voice (as the percentage of the detailing effort of one company, on the sum of the detailing efforts of all competitor companies for a specified class). One interesting conclusion drawn from Liu et al (2016) was that it is more profitable for a pharmaceutical company to detail a physician, when its competitors' detailing activity is low at that physician. The opportunity to cause a higher impact on the number of prescriptions is therefore higher in these cases. Liu et al (2016) assumed, in their research, that competitive detailing implies that companies know competitors' detailing activities applied in the past periods. Companies such as IQVIA (former IMS Health and Quintiles, before the merger of the two companies in 2017) provide such competitive information on promotion tools investments, including detailing (a study called ChannelDynamics^{TM}), on an aggregate or disaggregate basis.

Rao & Yamada (1988) had already addressed the concept of competitive detailing. In their research, they had access to data on detailing and detailing share. By multiplying the two, they obtained the competitive detailing investments for each firm, that is, the investment magnitude in detailing for each competing firm. They found that competitive detailing (the increase in detailing of a specific drug) «*is most effective against drugs that are very frequently prescribed*» (p. 749). By other words, «*the more a drug is prescribed, the more opportunities there are for brand switching*» (p. 744). Gönül et al (2001) already addressed,

albeit indirectly, the concept of competitive detailing, underlining the importance of having a data set that includes competitive promotion information about manufacturers. Mizik & Jacobson (2004) too emphasized that competitive detailing analysis implies having access to data on competitive promotion tools investments (such as detailing, drug sampling, and other), and Manchanda et al (2005) underlined the need of further research in the scope of competitive detailing.

Dong, Manchanda & Chintagunta (2009), using nominative data from a panel of physicians (on acid reflux disease market), found that competitive detailing impacts the number of prescriptions of drugs, affecting them adversely. The higher the intensity of competitors detailing, the lower the sales of the own brand. Figure 5.8 below evidences this effect. Dong, Manchanda & Chintagunta (2009) noted that competitive detailing effects are different for different competitor brands, as seen in figure 5.9.

	Nexium	*Prevacid*	*Aciphex*	*Protonix*
Nexium	.115	.000	–.045	–.014
Prevacid	–.027	.128	–.002	–.004
Aciphex	.007	–.017	.131	–.050
Protonix	–.039	–.002	.039	.120

Figure 5.8 – Cross detailing (mean) elasticities - competitive detailing

Source: Dong, Manchanda & Chintagunta (2009)

As noted by Dong, Manchanda & Chintagunta (2009), while Prevacid detailing has a very small effect on Nexium prescriptions, Aciphex has a much stronger effect. Another relevant conclusion pointed by Dong, Manchanda & Chintagunta (2009) was that the competitive effects were the strongest in the zero to two details range (number of details per quarter), as can be seen in figure 5.9.

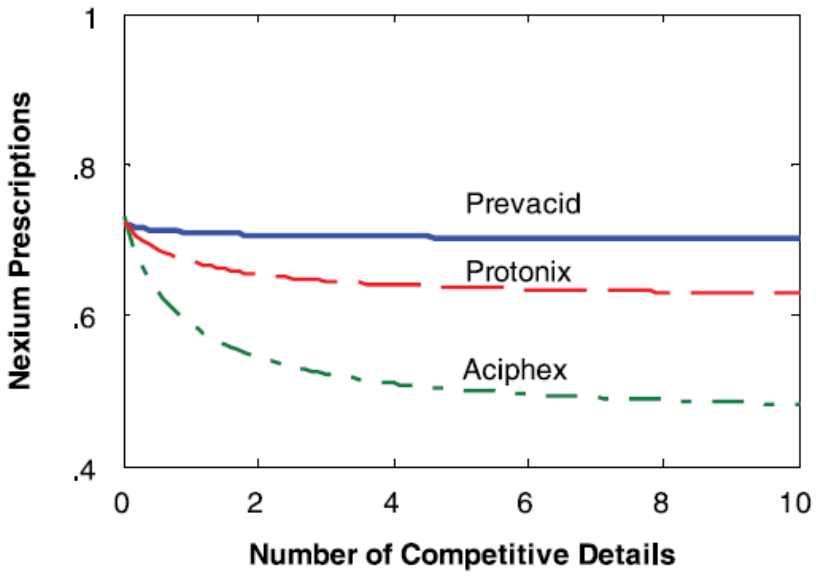


Figure 5.9 – Competitive detailing effects

Source: Dong, Manchanda & Chintagunta (2009)

Leeflang & Wieringa (2010) used not only brand detailing, but also competitive detailing (adapted Rizzo OLS regression model) to study the impact of several variables (including detailing, advertising and direct mail) on prescription drug sales. This adapted model had already been used by Windmeijer, de Laat, Douven & Mot (2006), when they analyzed the effect of several variables in drug demand (measured as defined daily doses, or DDD). They found that promotion expenditures (aggregation of detailing – the most representative promotion tool -, advertising, and direct mail) have an elasticity of 0,3, while the competitive promotion expenditures (made by competitors) have an elasticity of -0,12. They noted, about these results, that «*a sizeable proportion of promotion efforts is about establishing or maintaining market share*» (p. 20).

Liu et al (2016) also found that changes in competitive detailing may affect competitors' market shares. Using counterfactual simulations testing several detailing restriction policies, they estimated that detailing leaders would suffer the highest reduction in share of voice and market share (against other competitors and generics, when available).

5.5.1.4.Approach to research on detailing

Most of the papers covering the effect of detailing on prescription behavior analyze the association between call activity and the number of prescriptions using US-based data, as can

be drawn from Wazana (2000), Kremer et al (2008), and Spurling et al (2010) reviews. The number of papers covering the effect of detailing on physician prescription behavior using European-level data is limited, mainly targeting, at single country level, the Netherlands (Greving et al, 2006; Windmeijer, de Laat, Douven & Mot, 2006; Wieringa & Leeflang, 2013), France (Auvray, Hensgen & Sermet, 2003; Verdoux, Cougnard, Grolleau & Begaud, 2005), the UK (Freemantle, Johnson, Dennis, Kennedy & Marchment, 2000; Prosser & Walley, 2003a), Belgium (Berings, Blondeel & Habraken, 1994), and Spain (Caamano, Figueiras & Gestal-Otero, 2002). Moreover, the great majority of these authors using European-level data do not use longitudinal, time series data, with some exceptions such as Auvray, Hensgen & Sermet, 2003, Windmeijer, de Laat, Douven & Mot, 2006, Leeflang & Wieringa (2010) and Wieringa & Leeflang (2013). The others used cross-sectional data and experiments such as randomized control trials.

These papers can be grouped into two categories, using Spurling et al (2010) classification in their tables: the first category encompasses studies that specifically analyzed the effect of detailing on the prescribing frequency (Berings et al, 1994; Caamano et al, 2002; Verdoux et al, 2005). Berings et al (1994), evaluating three intervention groups of GPs in Belgium, in the scope of benzodiazepines prescription, observed that the tendency to prescribe benzodiazepines was associated with the utility of commercial information provided by pharmaceutical companies, and by the number of pharmaceutical sales representatives received. Caamano et al (2002) analyzed 234 self-administered survey questionnaires to Spanish primary care physicians in Galicia, addressing the perception of physicians on the quality of information about drugs obtained from pharmaceutical sales representatives (and other marketing instruments), and the influence of this information on drug selection. They found that physicians who gave more weight (in a Likert scale) to the information provided by pharmaceutical sales representatives evidenced a larger number of prescriptions. However, the number of pharmaceutical sales representatives received by physicians showed no relation to drug prescription quantities, suggesting that PSRs' credibility is more important than the number of visits. Verdoux et al (2005) analyzed 848 anonymous self-administered survey questionnaires returned from French GPs and found that physicians who declared having received a visit of a pharmaceutical representative promoting a newer antipsychotic drug in the previous month were more likely to have initiated an antipsychotic drug treatment during the previous month (odd ration of 3,06, 95% confidence interval).

The second category contains studies that analyzed the effect of total promotion investment (sum of all commercial investments including detailing) on the prescribing frequency (Freemantle et al, 2000; Auvray et al, 2003; Windmeijer et al, 2006; Greving et al, 2006; Wieringa & Leeflang, 2013). Freemantle et al (2000) studied the results of collaboration between a UK Health Authority and pharmaceutical companies to influence prescribing decisions of an intervention group consisting of 140 physicians, on proton pump inhibitors. They found that the pharmaceutical sales representatives' visits delivering the agreed marketing evidence-based guidelines pre-defined by the Health Authority did not produce a significant impact on prescribing behavior attributable to the intervention. Auvray et al (2003) analyzed the correlation between prescription and promotional investments data regarding new drugs launched in France from two therapeutic classes (antidepressants and antibiotics) and concluded that there was a strong correlation between the total investments made by pharmaceutical companies, and the number of prescriptions by quarter. The correlation between the number of prescriptions and investments in detailing separately was however not addressed, but appeared to be much lower, if existent (based in the interpretation of one chart showed in the article).

Windmeijer et al (2006) studied the responses by GPs to drug promotion activities by pharmaceutical companies in The Netherlands. They analyzed a set of aggregated data including prices, promotion investment, and prescriptions for the years 1994 to 1999 for 11 therapeutic classes, and found that promotion expenditures (consisting of the sum of detailing, advertising and direct mail) shifted the demand curve outwards, suggesting that a considerable percentage of promotion investments is directed at establishing market share. Greving et al (2006) combined data from a survey sent to GPs and a retrospective database consisting of prescribed drugs (including angiotensin II receptor blockers, or ARBs) by those physicians, in The Netherlands, and using a multilevel logistic regression found that GPs who reported frequent use of commercial information sources (comprising pharmaceutical sales representatives, journal advertisements, direct mailings, and sponsored meetings) were more likely to prescribe ARBs routinely, versus other antihypertensive drugs. Using a qualitative approach, Prosser & Walley (2013a) conducted 30 semi-structured interviews with 30 GPs in the UK. In this research, they suggest that high drug prescribers' relative willingness to prescribe new drugs may be shaped by the pharmaceutical industry. This article does not offer, however, quantitative evidence for this suggestion. As seen before, Wieringa & Leeflang (2013), studying several products in the Dutch market, found that the impact of

marketing efforts (including detailing) is significant for only a small portion of the brands, and are moderate in size.

Some conclusions can be drawn from these articles which used European-level data, which used manily cross-sectional data: in both categories the association between detailing quantity and drug prescription quantities is not undisputed. In the first category, two articles suggest an association between detailing quantity and an increase in drug prescription (Berings et al, 1994; Verdoux et al, 2005) and one article suggests the inexistence of a significant association between the number of reps received and drug prescription quantity (Caamano et al, 2002). In the second category, three articles present empirical evidence of an association between total marketing investments and prescription behavior (Auvray et al, 2003; Windmeijer et al, 2006; Greving et al, 2006), one shows no evidence of such association (Freemantle et al, 2000) and one presents evidence of a moderate association, but only in specific drug brands (Wieringa & Leeflang, 2013).

These findings, especially the ones from the first category using separate detailing data, appear to be partially different from finding generated by research using US-level data by authors such as Gönül et al (2001), Manchanda & Chintagunta (2004), Mizik & Jacobson (2004), Narayanan et al (2005), Datta & Dave (2016), among others. Limited research has been developed analyzing data from more than one country. Chintagunta & Desiraju (2005) analyzed the detailing behavior and impact on drug revenues in a group of five countries (US, UK, France, Germany and Italy), using data regarding three antidepressant drugs. They found that drug detailing elasticities are quite similar in three of the countries, and substantially higher in two of the countries. While the US, Germany and Italy evidence own detailings elasticities ranging from 0,17 to 0,32 (depending on the drug), the UK evidenced own elasticities in the 0,55 to 0,59 range, and France in the 2,32 to 2,43 range. Equally relevant was the outcomes of the ROI calculation, measured as the increment in revenues caused by an increase of US $1 in detailing: Germany and Italy evidenced noticeably lower ROIs (ranging from $0,56 to $1,79), the US and the UK showed intermediate values (oscillating between $4,58 and $9,13), and France evidenced prominently higher values (from $5,22 to $19,3).

These results suggest that different structures, regulations, health sector institutional frameworks, as well as potential different cultural and economic realities (that might differ considerably across the targeted countries) may well highlight the interest in the development of additional research using European-level data, where diverse results on the outcomes of the association between detailing activity and drug prescription behavior can potentially be found.

It would be of interest a contribution to build empirical evidence whether the European pharmaceutical market is less or more responsive to marketing efforts than the US market, following Wieringa & Leeflang (2013) notes for future research. In fact, Wieringa & Leeflang (2013) had already underlined that «*the US pharmaceutical market may be more responsive to marketing efforts*» (p. 3398). Leeflang & Wieringa (2010) did not find statistically significant evidence that the elasticities of non-US countries are higher than the ones in US.

Previous research on detailing impact on prescription behavior has been made using both nominative and market (aggregated) level data. Nominative data on detailing frequency and prescription activity was used by several scholars including Narayanan et al. (2003), Dong, Manchanda & Chintagunta (2009), John (2008), Nair, Manchanda & Bathia (2010), Keppe & Stremersch (2016), and Liu et al (2016), to list a few. Nominative data is typically collected in countries where this individual-level approach to data is allowed, mainly the USA, from where most of the research in this field comes from. Other scholars have been using aggregate level data, which sums data from a region or territory (as the sum of detailing visits and prescriptions from a specific area). According to Manchanda et al (2005), aggregate data consists of «*sales (dollars or units measured as either new or total prescriptions) and marketing instrument data (dollars or units) for detailing*» (p. 305). They also highlighted that there is also aggregate data regarding physician meetings and events, free sampling, and journal advertising. They noted that aggregate data has been more available to academic researchers than nominative level data, and that research data is usually provided by market research firms such as IMS Health, or by large pharmaceutical manufacturers. Scholars using aggregate level prescription and detailing data include Narayanan, Desiraju & Chintagunta (2004), Narayanan, Manchanda & Chintagunta (2005), Rosenthal, Berndt, Donohue, Epstein & Frank (2003), Vakratsas & Kolsarici (2008), Leeflang & Wieringa (2010), and Wieringa & Leeflang (2013), to list a few.

5.5.1.5.Challenges to traditional detailing

Detailing, as a traditional promotion instrument, has been facing substantial challenges in the pharmaceutical industry, due to several factors or drivers. Detailing is a very expensive promotion instrument, as noted by Davidson & Sivadas (2003), referring a Cap Gemini Ernst & Young study, suggesting that traditional face-to-face detailing can cost between USD$150 and USD$200 per visit. Narayanan, Manchanda & Chintagunta (2003) suggested that marginal detail costs should be in the range of USD $60 and $100. Liu et al (2016) used an average value of $153 per detailing visit in their research, and Kappe, Venkataraman &

Stremersch (2017) noted that the average cost of an average detailing visit is $150, based on Quintiles records. These cost magnitudes per visit suggest that these figures, when multiplied by dozens or even hundreds of PSRs, may imply millions of USD dollars in fixed promotion costs (or semi-fixed, in the case of contract sales organizations).

The number of PSRs reps increased substantially from the nineties to the mid 2000's. According to Montoya (2008), there were 40.000 PSRs in the US market in 1996, and this number climbed to 85.000 in 2005, an increase of 112,5%. ZS Associates, which publishes regular commercial studies on PSRs number and access to physicians, calculated the number of PSRs in 2005 to be 102.000, then falling to 63.000 in 2014, a 38% reduction (ZS, 2014a). According to IMS Health (2016), the number of full-time equivalent (FTE) PSRs in the US was 68.998 in 2015 (declining 0,9% from 2014), and 71.164 in Europe top five countries (declining 2,7% from 2014). Globally, the worldwide number of PSRs was, according to IMS Health (2016), 450.539 (an increase of 0,1% from 2014). Figure 5.10 evidences the evolution of the number of PSRs in the USA, from 1996 to 2014.

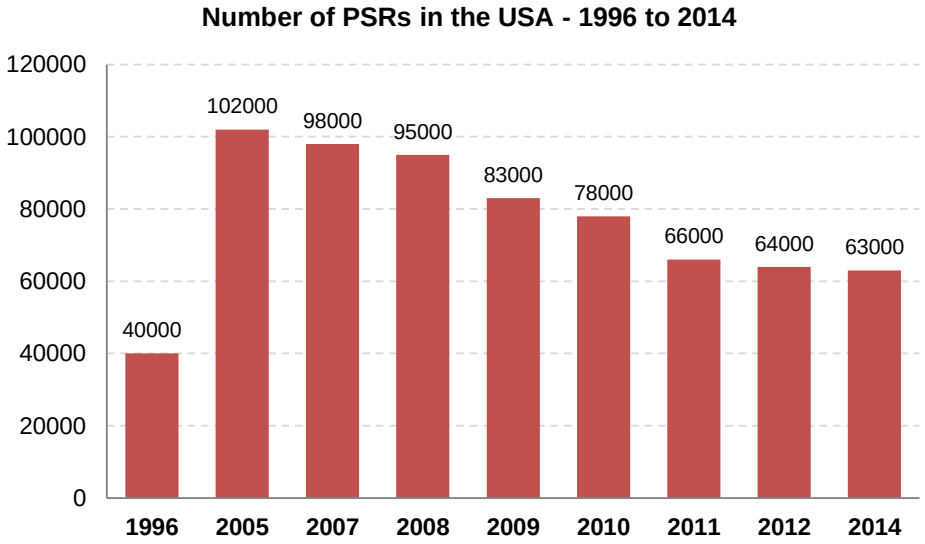


Figure 5.10 – Number of PSRs in the USA – 1996 to 2014

Source: ZS Associates

Considering the period of 1995 to 2005, while the number of PSRs more than doubled, the number of active physicians only increased 18% (from 625.443 to 762.438, according to Statista, 2017a), which generated more pressure on PSRs and on physicians. As a result, the average duration of a PSR sales call has fallen, as covered above, from eight minutes in 1997 to between three to four minutes in 2001 (Yi, Anandalingam & Sorrell, 2003; Bernewitz,

2001). Trucco & Amirkhanova (2006) addressed this increased competition between PSRs for physicians' time, which provoked a reduction in the detailing return on investment, realizing that, with more compressed sales calls, PSRs may not be able to promote four products (details) in their portfolio, ending in many situations presenting one detail only, in each visit.

From the year 2005, the decline in the number of PSRs may be related to the lower economic return on R&D investment. According to McKinsey (2012), who studied the R&D for top 10 biopharma players, the return of R&D investments has been falling since the nineties, a tendency aggravated in the 2000's (figure 5.12). Carter (2005) had already noted that many pharmaceutical companies are experiencing a drop in R&D productivity (figure 5.11).

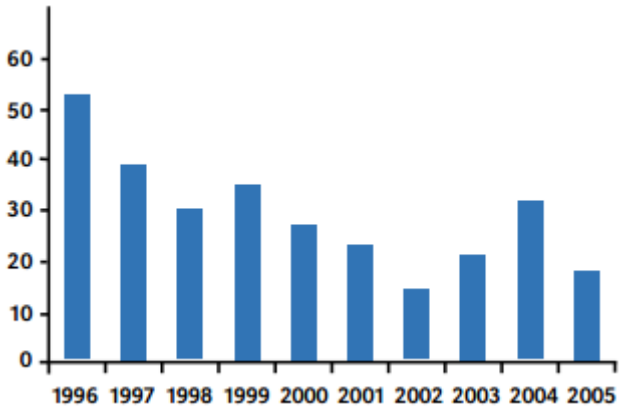


Figure 5.11 – New compounds approved by the FDA

Source: Carter (2005)

Yet, the evolution on the number of PSRs appears to evidence some resistance from companies, from 2011. A possible explanation may be companies' fear of losing share of voice by reducing the number of PSRs, while competitor companies may decide to keep their number of PSRs untouched (Zolterns, Sinha & Lorimer, 2004).

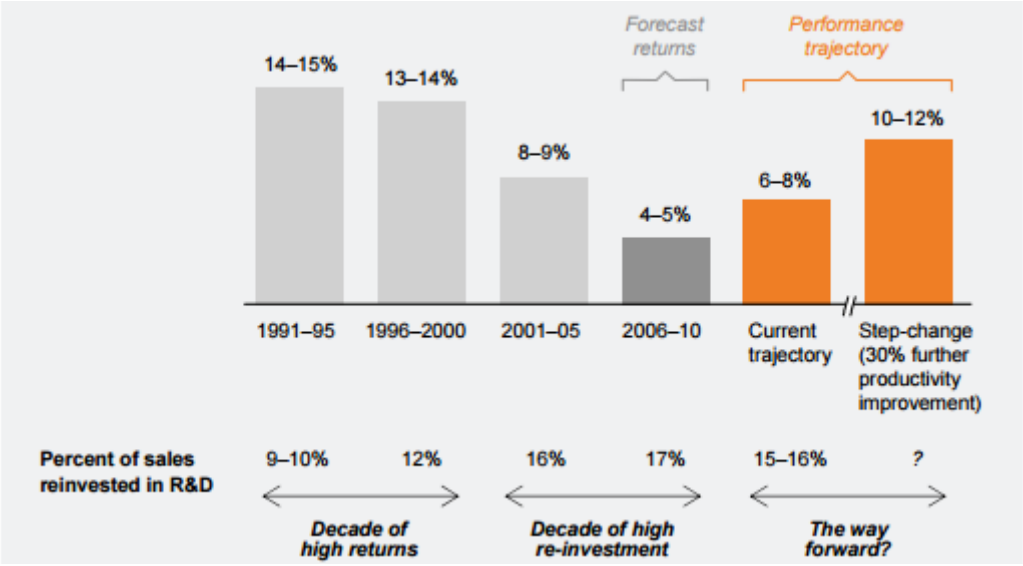


Figure 5.12 – Economic return on R&D investment for top10 biopharma players

Source: McKinsey (2012)

Other factors may have contributed to additional hurdles to traditional detailing. As stressed by Davidson & Sivadas (2003), managed care organizations (hospitals and other institutions), in an effort to increase their profitability, have been reducing the amount paid to physicians, «*forcing them to see more patients daily and leaving little time for sales representatives*» (p. 22), which may lead to PSRs to spend hours in hospitals and clinics waiting rooms and possibly not seeing any physician at all. Many PSR may not even be able to get past the receptionist (Alkhateeb & Doucette, 2008). Montoya (2008) also addressed the issue regarding doctors' time pressure, stating that, because Managed Care Organizations have been limiting the amount of physicians' reimbursements, they are forced to attend more patients, having much less time to receive visits from PSRs. This situation has been especially present in the case of high prescribing physicians, which gather the interest of most pharmaceutical companies, and end up being visited much more often than the average physician (Montoya, 2008). This increased physician opportunity cost and time pressure may erode the effectiveness of the interaction generated between PSRs and physicians, since by the one hand it may be difficult for the PSR to properly detail a physician in a short period of time, and by the other the physician's attention might not be easy to capture in such a situation (Davidson & Sivadas, 2003). Paired with this factor, some countries have already started to impose detailing restriction policies, limiting the access of PSRs to institutions and to physicians, such as in Portugal (this topic will be addressed in more detail, later in this thesis, as a separate chapter).

Finally, the advent of new technologies and promotion tools such as e-detailing, much more convenient to physicians than traditional detailing (Alkhateeb & Doucette, 2008), and which can contribute to the share of voice of the promoted drugs, may also contribute to the discussion about the traditional detailing cost effectiveness.

5.5.2. Drug sampling

Williams & Hensel (1991) explained that drug sampling is the «*provision of small amounts of pharmaceuticals to physicians*» (p. 48). Drug sampling occurs when pharmaceutical sales representatives dispense drugs samples to physicians (Mizik & Jacobson, 2004), that they will use at their practices (offering them to patients). Parsons & Abeele (1981) noted that samples are distributed by PSRs and have the purpose of familiarizing doctors with a drug, providing them with starter doses. They also noted that samples are well seen by doctors and seen as a service since patients can benefit from them by beginning treatments immediately, and samples give doctors the opportunity to evaluate a drug. Samples are usually distributed by medical representatives. Fugh-Berman & Ahari (2007) also evidenced that physicians appreciate samples, which can be used to reduce the cost of a prescription to a patient.

Williams & Hensel (1991) explained why pharmaceutical manufacturers provide samples to physicians. They noted that drug samples have been given altruistically so that physicians can give them to patients that otherwise would not be able to afford them, and to allow physicians to experiment the drug's alleged efficacy. Fugh-Berman & Ahari (2007) explained that the goal of providing drug samples is to gain entry into physicians' offices, and to habituate them to prescribing targeted drugs. The researchers also noted that even "sample-grabbers", that is, doctors who refuse or resist to receive PSRs, appreciate drug samples, and highlighted that patients tend to like an offer from their doctors. Fugh-Berman & Ahari (2007) also addressed an additional explanation to the doctors' willingness to receive samples: «*the convenience of an in-house pharmacy increases loyalty to both the reps and the drugs they represent*» (p. 624). As noted by Kumar & Panigrahi (2014), samples help physicians engage into a routine practice for the particular drug brand being sampled, helping them to recognize its name, which continues present in their minds. Drug samples are the second most important promotion instrument in terms of investment to pharmaceutical companies (IMS Health, 2015a), and are usually well accepted by physicians (Salmasi et al, 2016).

Drug sampling can have a significant and positive effect on the number of prescriptions. Mizik & Jacobson (2004), when studying the effect of detailing and drug sampling on new prescriptions, found that both promotion instruments yielded positive effects on the number of new prescriptions. However, detailing had a stronger effect, with coefficients (for the three brands analyzed) of 1,56 (brand A), 0,32 (brand B) and 0,153 (brand C) for detailing, and 0,155 (brand A), 0,039 (brand B) and 0,014 (brand C) for drug sampling, meaning that, in order to achieve one additional prescription, the number of sales calls (visits) should increase 0,64 (drug A), 3,13 (drug B) and 6,54 (drug C), and the number of drug samples should increase 6,44 (drug A), 25,64 (drug B), and 73,04 (drug C). Gönül et al (2001) also had demonstrated the positive effect of drug sampling on prescription behavior. When studying five years of data coming from a physician panel, they found that both detailing and drug sampling have a positive effect on the number of prescriptions of the promoted drug. The coefficients obtained using a multiple regression were 0,1085 for detailing and 0,0345 for drug sampling. Montoya, Netzer & Jedidi (2010), when studying data from a new drug in the USA, and with the goal of dynamically allocating detailing and sampling activities, found that drug sampling had a significant and positive effect on the number of prescriptions. They found that drug sampling elasticity was 0,253, while detailing elasticity was 0,654.

As covered above, sampling occurs when pharmaceutical sales representatives dispense drugs samples to physicians (Mizik & Jacobson, 2004), that they will use at their practices (offering them to patients). But sampling must be managed properly and target to the most interesting prescriber segments, since excessive sampling for an entire course of treatment could lead to sales cannibalization (Fugh-Berman & Ahari, 2007). Chimonas, Brennan & Rothman (2007), in their research using focus groups with physicians, studying the dynamics of the relationship kept with PSRs, underlined the importance given by physicians to the provision of drug samples. One of the focus group participants argued that «*sometimes you tend to return a favor when you get a lot of samples, thinking of patients who are self-pays. You tend to write a little more so they will come back and give you more samples*» (p. 187). On page 188, the researchers provide additional transcripts underlining the importance and influence of drug samples to physicians: «*They've got you because they gave you the samples, you [dispensed] it, you start a patient on the samples*» (p. 188), and «*The drug companies give them out for a reason...they want you to become accustomed to the medication. They want it embedded in your mind*» (p. 188).

5.5.3. Gifts and meals

Gifts are offers given by the sales representatives to physicians, and can be of small value, or higher value. These can include ballpoint pens, medical books, dinner out, spouse's meal at dinner, conference and/or travel expenses, free drug samples, and golf tournament fees (Jastifer & Roberts, 2009). Gifts can range from simple brand reminders such as stationery with manufacturer's name and product logo, to more expensive gifts, jewelry or iPads (Salmasi et al, 2016). Katz, Caplan & Merz (2010) suggest that even small gifts called reminder gifts (pens and notepads) and meals may influence doctors' drug choice. The researchers explore the effect of gifts on behavior, in the sense that gift recipients may feel the need to reciprocate, even if he or she is not aware or conscious that this may influence their behavior. According to Cialdini (1984), «*by virtue of the reciprocity rule, then, we are obligated to the future repayment of favors, gifts, invitations, and the like*» (p. 13).

Recent research has been made to assess eventual influence of gifts and meals from pharmaceutical industry and the effect on physicians' prescriptions. King & Bearman (2017) studied the association between prescription of psychotropic medications and gifts receiving. They found that the uptake of new expensive medications was significantly lower in US states with marketing regulation, when compared to states allowing unrestricted pharmaceutical marketing. In states that were banning all gifts, the drop in market shares ranged from 39% to 83%. The conclusions also suggested that gift bans and gift restrictions were much more powerful in terms of prescription reduction, than disclosure policies. DeJong et al (2016) studied the impact of pharmaceutical industry-sponsored meals and physician prescribing patterns for Medicare beneficiaries, finding an association between the receipt of those meals (with an average value of less than US$20) and an «*increased rate of prescribing the promoted brand-name medication relative to alternatives within the drug class*» (p. E8).

5.5.4. Direct-to-consumer advertising

DTCA is directed at impacting the consumer or user of a drug, as noted by Salmasi, Ming & Khan (2016). DTCA in prescription drugs is only permitted in two countries in the world (USA and New Zealand), as highlighted by Liang & Mackey (2011). It can be used to impact consumers via several traditional communication channels, including television, newspapers and magazines (Iizuka & Jin, 2005). DTCA was facilitated in the USA since August 1997, when the FDA mitigated the restrictions on this type of promotion instrument, as noted by Bala & Bhardwaj (2010).

DTCA can not only influence patients' behaviors but also physicians' prescription choices. While some research suggests that higher DTCA expenditures may increase the number of visits to doctors (Iizuka & Jin, 2005), other find strong evidence that DTCA can influence physicians' drug choices when prescribing. For instance, Kravitz et al (2005) found that patients' requests to physicians for a specific drug brand have a strong effect on physician prescribing in major depression and adjustment disorder pathologies. Liu & Gupta (2011), in their analysis of DTCA expenditures effects using data from the anti-hyperlipidemic market in the US, found that DTCA has a positive and long-term effect on the number of visits to physicians by newly diagnosed patients. They also found that own-brand DTCA expenditures increase the number of patient requests for two of the three drug brands analyzed. Bala & Bhardwaj (2010) noted that DTCA appears to have two distinct effects: to inform patients that there as drugs to treat specific diseases (constructive, as a market expansion), and to persuade patients to request specific drug brands at their visits to physicians (combative, in an attempt to increase market share). More recently, Mukherji, Jaimakiraman, Dutta & Rajiv (2017), analyzing the impact of a policy change in DTCA in the US (prior DTCA 1992-1997 and post DTCA 1998-2001) in the sales of four cholesterol-reducing drugs (statins), suggested that DTCA led to category expansion as well as enhanced sales of each brand. Figure 5.13 evidences the conceptual map of potential DTCA effects on patients' actions for a chronic disease.

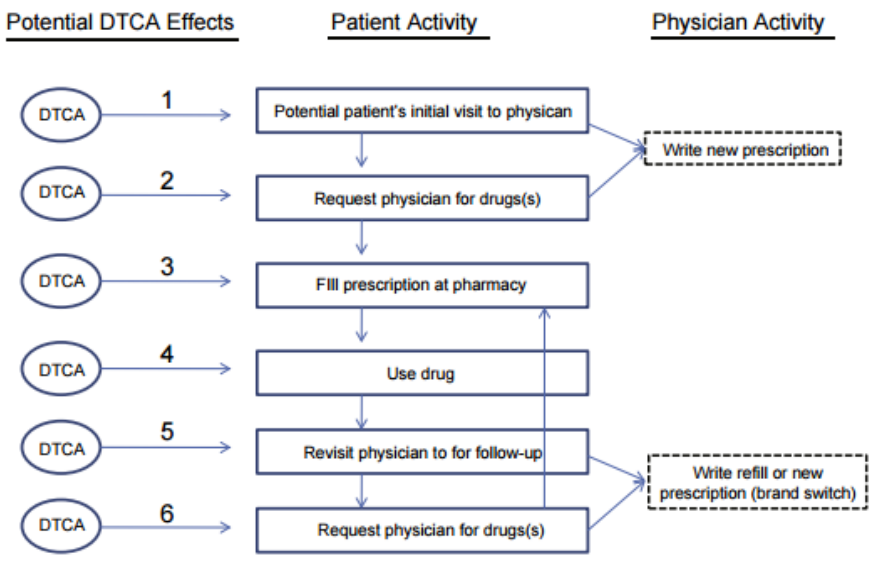


Figure 5.13 - Conceptual map of potential DTCA effects on patients actions for a chronic disease

Source: Liu & Gupta (2011).

In the US pharmaceutical industry, DTCA represented $800 million in 1996, reaching $4,2 billion in 2005, as underlined by Bala & Bhardwaj (2010). A report developed by ZS Associates (figure 5.14), compiling information from several sources including Nielsen, Kantar, and IMS Health, evidences the evolution of DTCA investments in the USA, in the period of 1997 to 2015 (ZS, 2016b). In 2016, the investment in DTCA had reached $6.4 million, according to Kantar Media (2017).

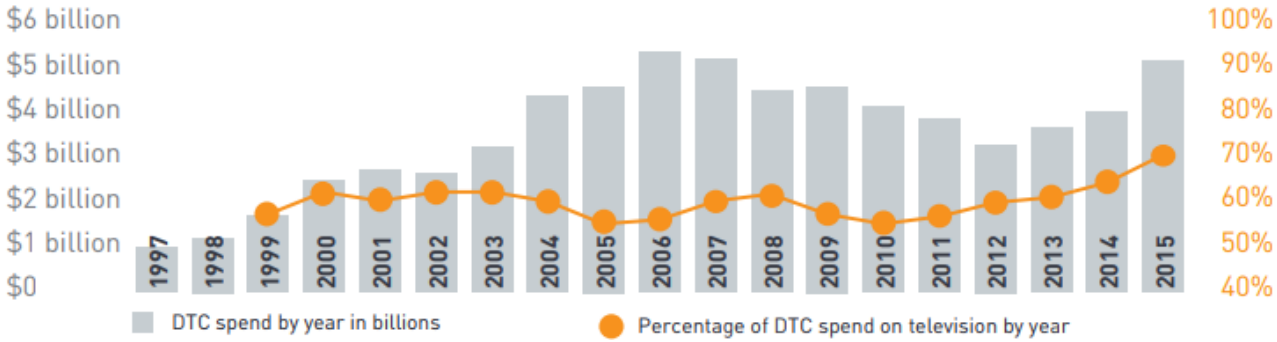


Figure 5.14 – Evolution of investment in DTCA in the US

Source: ZS (2016b)

5.5.5. Medical journal advertising

Medical journal advertising, as underlined by Montgomery & Silk (1972), consists of advertisements placed in medical publications. Othman, Vitry & Roughead (2010) underlined that pharmaceutical companies use advertisements in medical journals with the goal of sharing medicine information to physicians, and that the disseminated medical information comprises product characteristics, marketing claims, and references to support the communicated claims.

Parsons & Abeele (1981) suggested that medical journal advertising «*enables the manufacturer to target doctors by specialty, is the least expensive medium in terms of theoretical potential exposures, allows repeated use of the same material to gain awareness, and provides a supportive editorial environment*» (p. 108). Medical advertising can include advertising in journals and direct mail advertising (Pitt & Nel, 1988). Williams & Hensel (1991) concluded, after their review on pharmaceutical promotion instruments, that this promotion instrument was found to have either a positive or no significant influence on physician prescribing behavior. But research conducted by Montgomery & Silk (1972), when studying dynamic effects of marketing communication expenditures (journal advertising,

direct mailing, and samples and literature), found evidence of positive elasticities of journal advertising both in the short (0,146) and the long run (0,365).

5.5.6. Direct mail advertising

As noted by Williams & Hensel (1991), direct mail advertising was one of the promotion instruments that received the earliest attention in the scientific literature.

Parsons & Abeele (1981) discussed the value of direct mail, which involves «*medical publications, reprints, leaflets, brochures carrying product information, and letters with new drug announcements*» (p. 108). Direct mail is, as underlined by Parsons & Abeele (1981), the quickest tool to reach a total target population (for instance a medical specialty universe, granted that an address list of all physicians is available), can be a tool of special interest to complement the PSRs detailing activities covering non-detailed products (medicines not included in the presentations), and can allow a segmentation by geographic area, physician age, specialization, prescription habits (when nominative prescription information is available). Since many companies use direct mail to promote medicines to physicians, these can dislike this promotion tool. The promotion instrument may appear to be declining as a source of pharmaceutical information to physicians (Williams & Hensel, 1991).

Direct mail advertising may have a positive effect on the number of prescriptions. Leeflang, Mijatovic & Saunders (1992) analyzed the effect of detailing, medical journal advertising and direct mail advertising. They found that a promotion category which included the sum of the investments in medical journal advertising and direct mail advertising had a positive effect on the number of prescriptions (detailing had also a positive, stronger effect). The isolated effect of direct mail advertising was however not able to quantify, due to the referred data aggregation. Leeflang & Wieringa (2010), analyzing data from the Dutch pharmaceutical industry for 49 drug brands, studied the effect of three promotion tools, consisting of detailing, medical journal advertising, and direct mail advertising. They found no significant coefficients for the majority of the brands, but for the ones where the coefficients were significant and with the correct (positive) sign, direct mail advertising had the lowest mean coefficient (0,007, comparing with 0,014 for detailing and 0,027 for medical journal advertising). Montgomery & Silk (1972) also found, when analyzing the dynamic effects of marketing communication expenditures (journal advertising, direct mailing, and samples and

literature), that direct mail advertising had the lowest elasticity (0,018 for long-run) among the three promotion instruments analyzed.

5.5.7. Continuing medical education & event sponsoring

Sponsored continuing medical education (CME) is another promotion instrument used by pharmaceutical manufacturers to impact physicians. Davidoff (1997) defined continuing medical education (CME) as the opportunities and mechanisms which allow medical practitioners to keep up to date in practice, by formal programs. Davidoff (1997) explained that CME involves «*hundreds of thousands of faculty and learners hours, and hundreds of millions of dollars, each year*» (p. 16). He also explained that there are two types of CME: formal, and informal. While the formal system runs under standards created and imposed by the Accreditation Council on Continuing Medical Education (ACCME), which exerts a central control and supervision, and participants receive CME credits on a hour-for-hour basis, the informal CME is characterized by «*local, distributed control that rests principally with individual physicians and health care organizations; no consistent or national criteria for educational credit; no formal requirement in connection with or credentialing (…) lack of definition of costs in time and dollars; and (so far) limited connection with industry*» (p. 15).

Manufacturers can interact with physicians in conventions, meetings and conferences, as noted by Evans & Beltramini (1986) and by Williams & Hensel (1991). These interactions can also take place at seminars and lectures or symposia organized or sponsored by pharmaceutical manufacturers (Pitt & Nel, 1981). Venkataraman & Stremersch (2007) noted that manufacturers can organize symposium meetings to present drugs and its efficacy and side effects to physicians. They found that these meetings have a significant and positive impact on prescription behavior (physicians attending more of these meetings prescribed significantly more of the drugs promoted in the meetings).

Conventions are usually events such as annual scientific meetings of professional societies, and medical specialty colleges, and meetings can be defined as an event from a local medical association with a pharmaceutical manufacturer representative (Evans & Beltramini, 1986). In their research, Evans & Beltramini (1986) found that when assessing the quality of information of conventions and conferences, physicians considered that the most important attribute was the reputation of speakers, and specialists tended to give more importance to these types of events than general practitioners. They also concluded that physicians tended to grant importance to the event organizer or sponsor. Evans & Beltramini (1986) also

concluded that physicians were likely to ask for product information after having participated in conventions and conferences, which confirms the potential of this instrument.

Events can have a promotion component if they are sponsored by a pharmaceutical manufacturer, and the speaker is paid by this company. But it can also be subject to a less direct promotion, should a series of situations occur, such as a low registration fee or none, free food, hospitality, or entertainment, or a pharmaceutical sales representative is present in the back of the room (as underlined by Noble (1992). Physicians can be granted funding for travel and registration to conferences or lodging for educational symposia and meals, as reviewed by Wazana (2000). Conference travel sponsorship can have a substantial impact on physicians' prescription behavior, as reviewed by Wazana (2000), highlighting that physicians who requested a sponsorship to a manufacturer are much more likely to prescribe the manufacturer's drug (several magnitudes versus non-sponsored physicians).

The pharmaceutical industry strongly supports CME for physicians, by providing industry-supported conferences, seminars, and symposia (Holmer, 2002). Relman (2008) suggested that the pharmaceutical industry sponsors more than 50% of the total CME initiatives. Steinbrook (2008) noted that CME initiatives supported by the pharmaceutical industry are usually free or funded for physicians attending to those initiatives.

One of the examples of a CME learning portal is Univadis, provider of online health care resources, where users (physicians and other health care practitioners) can register to have access to learning contents (Schroter et al, 2011). According to Univadis (2017) website, it is provided by Aptus Health, a Merck & Co subsidiary, which operates outside the US and Canada as Merck Sharpe & Dohme (MSD).

5.5.8. Other

Research funding exists when investigators receive funding in the scope of pharmaceutical industry affiliations, as noted by Bekelman, Li & Gross (2003). They noted that there is an association between industry sponsorship and pro-industry conclusions (odds ratio of 3,60), subject that will be addressed further in the topic **Ethical considerations**.

Engelberg, Parsons & Tefft (2014) analyzed the impact of payments to physicians and their prescription behavior relative to brands vs generics adoption. Studying the effect of payments including meals, gifts, speaking fees and other transfers of value, they found that doctors who received payments from the industry tended to evidence higher prescriptions of branded drugs over their generic equivalents.

Bergman (2017) studied the impact of payments typically associated with detailing activities on physician prescription behavior, using data collected from Centers of Medicare and Medicaid Services (CMS) and from Open Payments dataset. The payments data included transfers valued at $10 or more (in cash, products or services and consisted of food and beverage (the great majority, representing 96,4% of the payments, and 71,7% of the total payments value), education, speaking fees, honoraria, travel and lodging, and consulting fees. Bergman (2017) found that «*drug-related payments (which are associated with detailing) increase the likelihood that the physician would prescribe from the class of drugs*» (p. 31), and that «*physicians who stopped receiving drug related payments at a given year, were less likely to prescribe aminosalicylate drug therapy of any kind in the following years*» (p. 15), with reductions up to 9,2 percentage points two years after payments cessation, thus demonstrating a causal relation between payments and physician prescription behavior.

Carey, Lieber & Miller (2017) also found an association between payments to physicians and those physicians' prescriptions, when studying a combined dataset of Medicare Part D prescriptions and payments data (which consisted of especially meals, but also travel, speaking fees, consulting, gifts, honoraria, and payments related to research). By using a binary variable to represent whether a physician has received or not any payment, found that physicians receiving payments from a company were more inclined to prescribe drugs from that company.

5.5.9. Sub-chapter synthesis of main findings

This sub-chapter covered promotion tools using traditional communication channels, used by pharmaceutical companies to promote prescription medicines to physicians, but also to patients. These tools include detailing, drug sampling, gifts and meals, medical journal advertising, continuing medical education (CME) and event sponsoring, direct mail advertising, and direct-to-consumer advertising (DTCA). The first three involve a more personal interaction with physicians, whereas the others are less personal in nature.

The most important promotion instrument, both in terms of investment magnitude, and in terms of impact on prescription behavior, is detailing. Detailing is a form of personal selling and a form of relational marketing, where a pharmaceutical sales representative visits individual doctors, and provides information about his or her company's drugs. Detailing has been shown to impact physicians' prescription behavior. Table 5.3 presents definitions on detailing, and table 5.4 summarizes the evidences gathered from the literature review on detailing.

Table 5.3 – Detailing definition

	Brief description	**Theoretical grounding** (non-exhaustive)
Detailing definition	Face-to-face meetings where pharmaceutical representatives present information to physicians; each sales representative targets physicians in an effort to provide accurate and latest product information, and to encourage them in prescribing the presented prescription drugs for their patients who fit the specific diagnosis criteria	(Molloy et al, 2002; Yi, Anandalingam & Sorrell, 2003; Mizik & Jacobson, 2004)
	Detailing involves direct visits from drug company representatives to individual doctors, during which the representative would provide information about their company's drugs, free samples, scientific literature, trying to combat the efforts of PSRs from competing companies	(Rao & Yamada, 1988; Steinman, Harper, Chren, Landefeld & Bero, 2007)
	Detailing is a form of personal selling (sales theory point of view), and a form of relational marketing (marketing theory point of view)	(Fischer & Albers, 2010; Gronroos, 1994)

Source: own elaboration

Table 5.4 – Evidences gathered from the literature on detailing

	Brief description	**Theoretical grounding** (non-exhaustive)
Evidence on detailing	Detailing is the pharmaceutical promotion tool with highest total investment magnitude, used by pharmaceutical manufacturers to interact with physicians	(Yi, Anandalingamb & Sorrell, 2003; Gagnon & Lexchin, 2008; Datta & Dave, 2016)
	The effect of detailing on brand prescriptions is significant and on average positive, but modest	(Kremer, Bijmolt, Leeflang & Wieringa, 2008; Stremersch & Van Dyck, 2009; Stremersch & Lemmens, 2009)
	Detailing appears to be the promotion instrument that generates a higher effect on prescription behavior	(Pitt & Nel, 1988; Berndt, Bui, Reiley & Urban, 1995; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kalyanaram, 2008; Kremer et al, 2008; Kalyanaram, 2009; Dave & Saffer, 2012)
	Detailing appears to reduce price elasticity of drugs (reduces physicians' price sensitivy)	(Rizzo, 1999; Gönül et al, 2001; Narayanan et al, 2004; Windmeijer et al, 2006)
	Detailing effect on prescription behavior seems to evidence diminishing marginal returns	(Berndt et al, 1995; Gönül et al, 2001; Yi, Anandalingam & Sorrell, 2003; Manchanda & Chintagunta, 2004; Dong, Manchanda & Chintagunta, 2009; Yi, 2008; Liu, Gupta, Venkataraman & Liu, 2016)
	Detailing efforts appear to have a higher effect on prescriptions at the initial stages of the product life cycle	(Narayanan et al, 2003; Manchanda, Rossi & Chintagunta, 2004; Manchanda & Honka, 2005; Narayanan et al, 2005; Dave, 2013)
	Detailing seems to evidence carry-over effects	(Narayanan et al, 2004; Zoltners, Sinha & Lorimer, 2004; Yi, 2008; Montoya, Netzer & Jedidi, 2010; Liu, Gupta, Venkataraman & Liu, 2016)
	Detailing effect on prescriptions appears to be more on drug shares, rather than on drug category volume	(Narayanan, Desiraju & Chintagunta, 2004; Datta & Dave, 2014)
	Detailing may have different effects on prescription, depending on the type of payer (physicians mostly seeing patients with private health insurance seem to be more prone to be influenced by detailing)	(Gönül et al, 2001; Datta & Dave, 2014)
	Detailing elasticities depend on the therapeutic or disease classes	(Kremer et al, 2008; Stremersch & Van Dyck, 2009)
	Detailing may have a different impact on different medical specialties (specialists vs generalists)	(Chung, Kim & Park, 2017)

	Brief description	Theoretical grounding (non-exhaustive)
Evidence on detailing	Detailing may be linked with physician nonrational prescription behavior	(Haayer, 1982; Wazana, 2000; Brax et al, 2017)
	Detailing effect may be leveraged by selecting the right key opinion leaders to impact (social multiplier)	(Nair, Manchanda & Bhatia, 2007; Meffert, 2009)
	Gifts and meals associated with detailing may impact prescription behavior	(Katz, Caplan & Merz, 2010; Engelberg, Parsons & Tefft, 2014; DeJong et al, 2016; Bergman, 2017; Carey, Lieber & Miller, 2017; King & Bearman, 2017)
	Recipients of the detailing activities (prescribers) do not consider themselves as influenced as their colleagues	(Steinman, Shlipak & McPhee, 2001; Sah & Fugh-Berman, 2013; Riese et al, 2015; Salmasi et al, 2016)
	Detailing effectiveness can be optimized, in order to reach higher levels of sales force efficiency	(Yi, Anandalingam & Sorrell, 2003; Manchanda, Rossi & Chintagunta, 2004; Montoya, Netzer & Jedidi, 2010; Kappe & Stremersch, 2016)
	Certain physician profiles and situations increment the likelihood of a more frequent interaction between physicians and PSRs	(Alkhateeb, Khanfar, & Clauson, 2009; Gönül & Carter, 2012)
	Detailing effectiveness can be attenuated by a form of detailing called academic detailing	(O'Brien et al, 2007; Grande, 2009; Fischer & Avorn, 2012)
	Detailing efforts performed by competitor drug brands (competitive detailing) affect own brand number of prescriptions	(Dong, Manchanda & Chintagunta, 2009; Liu, Gupta, Venkataraman & Liu, 2016)
	Direct-to-physician promotion – from which detailing is the most important component – can have an impact on companies' stock returns	(Osinga, Leeflang, Srinivasan & Wieringa, 2011; Dingus, 2014; Dingus, Agnihotri & Hu, 2017)
	Detailing efforts can have spillover effects (in other drug categories not promoted, and in drugs prescribed with the focal brand in combination therapies)	(Dong, Chintagunta & Manchanda, 2011; Liu, Liu & Chintagunta, 2017)

Source: own elaboration

Research on detailing is relatively recent, with the majority of articles written since the early 2000s, and using mainly US-based data, with access to nominative-level data. European research is less common, with some papers published using Dutch, French and Spanish data.

Detailing faces several challenges as a pharmaceutical promotion tool. It is quite expensive, representing a strong burden of fixed costs. Access to physicians has increasingly been more and more difficult, since the huge increase in the number of PSRs was not accompanied by a proportional increase in the number of physicians. This situation put additional pressure on the average duration of a PSR visit, challenging the return on investment of this promotion tool. An additional hurdle to detailing is the lower payment hospitals and other institutions are giving to doctors, forcing them to see more patients, letting less time to receive PSRs. Another challenge is the implementation of detailing restriction policies in some countries, limiting the access of PSRs to institutions and to physicians. These challenges can pose both a threat and an opportunity to pharmaceutical manufacturers, since with the advent of new technologies, a newer version of detailing – e-detailing – may be explored.

Drug sampling is typically used in conjunction with detailing and is aimed at providing doctors with drug samples for their use with patients, familiarizing the former with a drug, and allowing access to physicians' offices. Drug sampling has been demonstrated to impact physicians' prescription behavior in favor of the offered drug samples. Gifts and meals are another tool that is generally used in the scope of detailing. Gifts can range from a small reminder ruler or ball pen, to more expensive gifts such as fees for conference or events participation. Both gifts and meals have been shown to influence physician prescription behavior. Medical journal advertising is one of the least expensive promotion tools, and direct mail advertising can reach a substantial number of physicians, complementing detailing activities. Continuing medical education has been used by pharmaceutical manufacturers to help physicians keep up to date in their practices, including funding for travel or lodging for educational symposia and meals). Direct-to-consumer advertising can be used in the USA and in New Zealand and has been demonstrated to impact both patients' behavior (increased number of visits to doctors, and request of specific drugs) and physicians' prescribing behavior (by accepting patients' requests to prescribe a specific drug).

5.6.Promotion tools using digital channels

This subchapter will address promotion tools using digital communication channels, which were allowed by the advent of information technologies. It will include e-detailing, e-sampling, healthcare portals, health social networks, e-mailing, online continuing medical education (CME), in a Web 2.0 philosophy.

5.6.1. e-Detailing

e-Detailing definition and characterization

Electronic detailing (e-detailing), as noted by Alkhateeb & Doucette (2008), was introduced by the pharmaceutical industry as a new communication channel to promote medicines to physicians. Alkhateeb, Khanfar, Doucette & Loudon (2009) defined e-detailing - a newer form of detailing - as the use of «*digital technology, such as internet, video conferencing, and interactive voice response, by which drug companies target their marketing efforts toward specific physicians with pinpoint accuracy*» (p. 98).

The cost of an e-detailing contact can be substantially lower than the cost of a traditional detailing interaction. Davidson & Sivadas (2003) noted, referring a Cap Gemini Ernst & Young study, that while traditional face-to-face detailing can cost between USD$150 and USD$200 per visit, an e-detailing interaction can cost only around USD$100. Trucco & Amirkhanova (2006) referred an initiative deployed by the company Lilly in the UK, in 2003, using live e-detailing, where live e-details were estimated to cost 80% of a traditional detail visit, but with a substantially longer duration (an average of more than 15 minutes per e-detail).

Characteristics of physicians using e-detailing

Alkhateeb & Doucette (2008), in their review, addressed commercial, non-peer reviewed studies where a physician profile of e-detailing was studied. They concluded that typical physicians using e-detailing are young (with less than 45 years old), that e-detailing usage by physicians is more common among physicians working in rural areas, and that e-detailing adopters usually tend to be higher prescribers, in contrast to their peers who do not use e-detailing. Alkhateeb & Doucette (2008) also stress the importance of gifts and incentives in the scope of e-detailing adoption. Moreover, they addressed the medical specialty as one important driver for the usage of e-detailing by physicians: primary care physicians appear to be more likely to use e-detailing, when compared to other medical specialties. Finally, they suggested that physicians working alone (solo practices) are more likely to use e-detailing.

Alkhateeb, Khanfar, Doucette & Loudon (2009) developed research to identify the characteristics of physicians targeted by the pharmaceutical industry to participate in e-detailing, using a survey of 671 physicians. They found, using a binary logistic regression model, that primary care physicians evidenced a higher likelihood to be targeted for e-detailing, versus other specialties. Older males, prescribing more than average, was also a significant predictor of higher probability to be invited to participate in e-detailing activities. Other significant explanatory variables were the frequency of pharmaceutical sales representative interaction (the higher the frequency, the higher the likelihood of being invited for e-detailing), peer influence (physicians with peers using e-detailing are more likely to be invited), and size of practice (doctors working in small practices are more likely to be invited).

Using the same study but analyzing additional variables, Alkhateeb & Doucette (2009) studied the influences on adoption of e-detailing by physicians, and found that the significant variables were perceived relative advantage (doctors who identify an advantage for obtaining drug information by using e-detailing are more prone to adopt it), peer influence (peers already using e-detailing can have a positive effect on physician adoption of e-detailing), attitudes (doctors who had attitudes such as credibility, understandability and applicability towards the usefulness of e-detailing were more likely to adopt e-detailing), type of specialty (primary care physicians appear to be more likely to adopt e-detailing, when compared to specialists), years in practice (doctors with less experience seem to be more prone to use e-detailing, than more experienced ones), and presence of restrictive policy for traditional detailing (doctors practicing in institutions that have restrictive access policies are less likely to adopt e-detailing, as well as detailing). Another interesting conclusion of this article was that physicians who are visited more frequently by traditional detailing are more likely to participate in e-detailing interactions (four fifths of the e-detailing users were from the group who met PSRs more frequently), which Alkhateeb & Doucette (2009) underlined could mean that physicians may consider e-detailing as a complementary channel to traditional detailing, but not a substitute channel.

Types of e-detailing

Alkhateeb & Doucette (2008), in their review of electronic detailing of pharmaceuticals to physicians, addressed two types of e-detailing: virtual (interactive) e-detailing, also known by self-detailing (Trucco & Amirkhanova, 2006), and video (live) e-detailing.

The former – virtual e-detailing, or self-detailing - was defined by Heutschi et al (2003), in their research on challenges of e-detailing in Europe, as an interactive multimedia experience that doctors access to, in a mixture of Flash-based online presentation and online training for a specific medicine. According to the researchers, the presentations can be subject to additional requests from the physicians, such as demand for additional information, request samples or ask for a face-to-face visit with a PSR (detailing). As underlined by Trucco & Amirkhanova (2006), in these self-contained multimedia presentations physicians can be exposed to information on medicines side effects, clinical trial data, and prescription guidelines, at their own pace and at the most suitable time for each physician. The usual duration of a virtual e-detailing presentation is between four and fifteen minutes: Alkhateeb & Doucette (2008) suggest the duration to be between four and eight minutes, Montoya (2008) suggests a duration of 10 minutes, Trucco & Amirkhanova (2006) suggest a duration of between five and fifteen minutes. Another source, closer to the e-detailing practice, advocates an average of eight minutes for a virtual e-detail presentation (Bernewitz, 2001).

The later – video (live) e-detailing – consists, as underlined by Alkhateeb & Doucette (2008), of a face-to-face PC-based video conferencing between a PSR and a physician. According to Heutschi et al (2003), with video e-detailing physicians PSRs and physicians communicate using computers with internet access, camera and microphone. They also noted that this type of e-detailing is closer to the personal traditional detailing in the sense that it also allows a high proportion of analogue communication elements such as image and speech. This type of e-detailing can be particularly useful to communicate with physicians based in more remote geographic areas who see very few PSRs, or physicians not allowed to receive PSRs at their practice (Alkhateeb & Doucette, 2008). In terms of duration of a video e-detailing, this interaction can last over 15 minutes on average, with some interactions reaching up to 30 minutes (Trucco & Amirkhanova, 2006), which represents several times the duration of a typical detailing interaction.

Drivers for the ascension of e-detailing

As reported by IMS Health (2015a), promotion tools using digital communication channels, including e-detailing, represented 3,2% of the total pharmaceutical industry investment in 2014, 59% of which allocated to e-detailing activities. Despite the strong growth rate (+37,2% from 2013 to 2014), e-detailing is still a marginal promotion instrument. In data published regarding the year 2015, IMS Health (2016) reported that digital channels weight increased to 3,8%, increasing 15% from 2014.

Several scholars have addressed the reasons for the growth of e-detailing as a promotion tool to impact physicians. Davidson & Sivadas (2003) proposed three reasons for this growth. The first reason consists of the increased physician use of the internet, turning the internet into a new channel that pharmaceutical companies can use to interact with physicians. The second reason is related to the increased opportunity costs of physicians (time premium), where pharmaceutical companies try to find alternative channels to keep their share of voice among physicians. The third reason pointed by Davidson & Sivadas (2003) has to do with the fact that pharmaceutical companies do not want to be left behind in the ascension of this digital channel, since many of their competitors already have deployed such digital interaction channels with physicians. They state that companies have fear of losing marketing share to competitors, by not "playing" digital.

Alkhateeb & Doucette (2008) underlined that a major factor explaining the ascension of e-detailing is its convenience to physicians. Other drivers pointed include time savings, ability to follow up (with a face-to-face visit) and the fact that e-detailing may be less disrupting that traditional detailing. In their review of e-detailing of pharmaceuticals to physicians, Alkhateeb & Doucette (2008) also highlighted that the quality of the information provided through e-detailing may be higher than the quality delivered through detailing, as well as its consistence in quality and quantity.

Gönül & Carter (2010) suggested that pharmaceutical companies may choose to use e-detailing as a «*way to overcome the challenge faced by sales representatives to meet with the physician at a time convenient for both parties, to meet for the desired length of time*» (p. 101).

Benefits of using e-detailing

Previously in this thesis, we addressed some challenges to traditional detailing. In this topic, we will now highlight some of the benefits of using e-detailing, which have been covered in the literature.

E-detailing can reach physicians at an hour of the day they typically are not working anymore. A study developed by Manhattan Research in 2005 concluded that physicians who engage into e-detailing do it between 8pm to midnight, as noted by Trucco & Amirkhanova (2006). QuintilesIMS (2016b) study on UK and Spanish specialists concluded that 57% of those using video e-detailing were at home. Trucco & Amirkhanova (2006) also addressed other benefits pharmaceutical companies can reach by using e-detailing. One benefit is that it can support or complement traditional detailing, helping fill gaps between PSRs visits, helping increase the share of voice of a drug amid online physicians, especially in the scope of a product launch. Another benefit is the ability, in the post-launch phase, to help correct positioning problems for drugs in complex indications, also allowing impacting physicians typically not visited with regular detailing, or out-of-target physicians. Another benefit referred by Trucco & Amirkhanova (2006) is the fact that e-detailing can offer a cost-effective communication for older of off-patent drugs that have lower budgets than newly launched strategic ones. Montoya (2008) also addressed why e-detailing is becoming more popular among pharmaceutical companies. He suggested that it «*maximizes the time of the sales force, cuts down the cost of detailing and increases physician prescribing*» (p. 635).

Physicians also recognize benefits of using e-detailing. QuintilesIMS (2016b) research on UK and Spanish specialists using e-detailing described the main benefits stated by doctors when using e-detailing. The four main benefits were: easier to reschedule contacts, fits well into doctors' schedules, saves doctors time versus face-to-face detailing, and able to download information from the online facility.

E-detailing impact on prescription behavior

In terms of efficacy, e-detailing also seems to impact physician prescription behavior, as noted by Gönül & Carter (2010), where pharmaceutical companies seem to benefit in terms of prescription from increasing both e-detailing and face-to-face detailing (with both standardized coefficients positive, 0,509 for detailing and 0,384 for e-detailing). There is however the need to optimally balance e-detailing and detailing to certain physicians, as the interaction of the two promotion instruments may produce negative outcomes. Montoya

(2008) has also addressed the efficacy of e-detailing, or return on investment (ROI) referring three commercial studies. The first was conducted in Japan by Aventis, with a control group (traditional detailing only) and a test group (traditional detailing and e-detailing), where the test group evidenced a substantially higher number of promoted drug prescriptions (between +19% and +25%), when compared to the control group, allowing e-detailing to reach a revenue:cost ratio of 3,2:1, while traditional detailing only reached a ratio of 2,5:1. The second was conducted by Physician Interactive, using a test group of more than five thousand physicians impacted by a e-detailing program that allowed an interaction between the PSR and the physicians, and resulted in a 63% increase in the prescription of the promoted drug. The third, also highlighted by Montoya (2008), was performed by iPhysicianNet and involved the company Novartis, and resulted in an increase of 58% in prescription volume of the drug subject to e-detailing, also increasing not only the average duration of the call, but also the number of drugs detailed.

Montoya (2008) summarized some differences between variables regarding traditional detailing and e-detailing. Table 5.5 shows these differences on ROI, reach to physicians, average length of interaction, and cost effectiveness of both promotion instruments. Gönül & Carter (2012) studied the physician profile more associated with heavy prescription potential for established and new drugs, and suggested that, for newer drugs, traditional detailing is not as effective as it is for more established drugs. In this scope, they proposed that pharmaceutical companies launching a new drug may want to try other forms of persuasion using alternative promotion tools, including e-detailing.

Table 5.5 - Traditional detailing versus e-detailing trade-offs

Traditional detailing	Criterion	E-detailing
Low	ROI	High
Difficult	Reach to physicians	Easier
Less	Average length of interaction	More
Low	Cost effectiveness	High

ROI: Return on investment.

Source: Montoya (2008)

It is of importance, as stressed by Alkhateeb et al (2009), that e-detailing may be more effective to use considering certain physicians characteristics such as specialty, age, prescription volume and gender.

5.6.2. e-Sampling

As addressed by Kumar & Panigrahi (2014), e-sampling (or on-line sampling, or on-line sample ordering) is an on-line technique by which doctors can apply for samples in a request form, using a laptop or mobile devices. This new way of managing drug sample requests from physicians has been changing the process of sample delivery, according to Kumar & Panigrahi (2014). They explained this relatively simple process: after physicians insert their drug sample requests, PSRs can analyze doctors' profile in terms of interest for particular drugs, allowing PSRs to adjust their products detailing, highlighting, during the visit with the doctors, trying to understand the reason for their interest in the drug samples' molecules. Drug requests can be made in health care portals which doctors can access, requesting drug samples directly from the manufacturer (Puschmann & Alt, 2001), or directly in pharmaceutical companies' websites. The information regarding e-sampling (nominatively by physician) can be integrated in CRM systems, as noted by Vecchione (2008). This can include drug molecule and medicine brand, number of samples requested, and historic drug sample request patterns).

E-sampling can play an important role not only in attracting physicians to the company website, but also to encourage them to engage into e-detailing, as noted by Doyle (2007). He referred an example of a company where drug samples were only freely available to the physicians that agreed to participate in an e-detailing program.

5.6.3. Company websites and healthcare portals

As covered before in the closed loop marketing section (CRM and SFA), healthcare portals (represented below in figure 5.15) are internet-based solutions that help connect several players on the pharmaceutical industry, allowing value creation not only to pharmaceutical companies, but also to several players such as wholesalers, pharmacies, institutions (hospitals and other), and physicians, permitting the provision of individualized products and services such as applications, content and services (Puschmann & Alt, 2001).

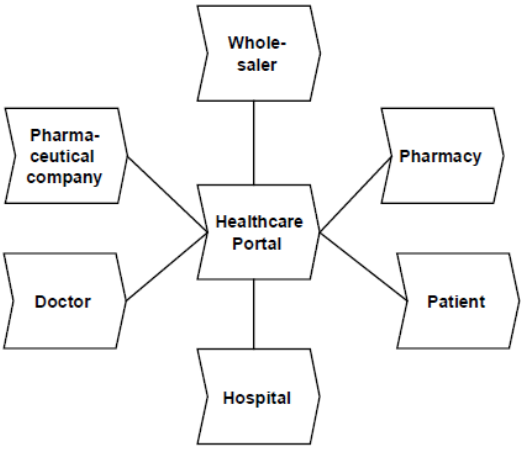


Figure 5.15 – Healthcare portals

Source: Puschmann & Alt, 2001

Healthcare portals can be classified into four types (Puschmann & Alt, 2001). The first is process portals, characterized by a web-based integration of services for one specific customer process. This is the case of the previously referred ePharma, a service provided by Grasshopper, a company operating in Portugal, allowing pharmaceutical companies to manage the whole process of medicine orders.

A second type of healthcare portal is information portals, which «*offer information about diseases, symptoms, medicines, etc. for professional users and patients*», as highlighted by Puschmann & Alt (2001, p. 4). They also noted that these portals' business models are usually based on advertising and can have a significant influence on the doctor-patient relationship, since they provide accessible information on diseases and methods of treatment, helping balance power between physicians and patients, in terms of information. Medical portals are an example of information portals, providing web-based medical community with access to medical information, as noted by Shepherd, Zitners & Waters (2000), which also highlighted that these portals can be public, or corporate. Research conducted by De Leo, LeRouge, Ceriani & Niederman (2006) in the United States found that the main portals physicians' access to gather medical information are Uptodate, Medscape, Webmd, Mdconsult and Emedicine. The researchers concluded that the vast majority of physicians (more than nine out of ten) tend to access a medical targeted site given their accuracy of on-line information, instead of using a generalist search engine. Figure 5.16 below presents a screenshot of one of these portals, Medscape.

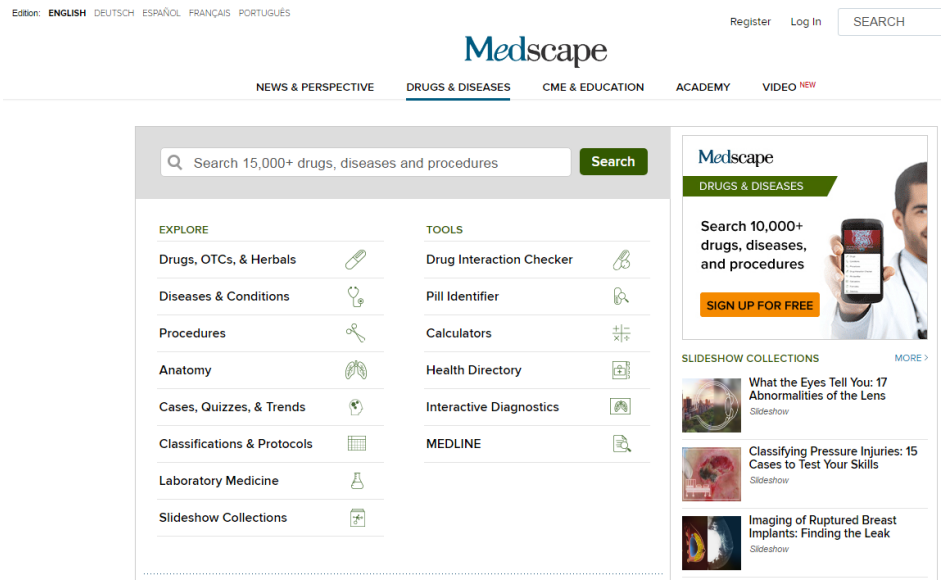


Figure 5.16 – Example of a physician portal – Medscape.com

Source: Medscape.com

Epocrates (www.epocrates.com), a pharmacopoeia, or drug information database, is one of the most popular handheld drug databases in the United States, as highlighted by Fischer, Stewart, Mehta, Wax & Lapinsky (2003). They explained that physicians can download these drugs databases for free, but their demographics and practice information may be sold to pharmaceutical companies, who sponsor the service. This service offers pharmaceutical companies the possibility of doing drug advertising at multiple points across the care continuum, as highlighted below in figure 5.17. The service allows, for participating brands, coupon delivery, voucher and co-pay offers post-prescription to qualified patients, and patient education programs.

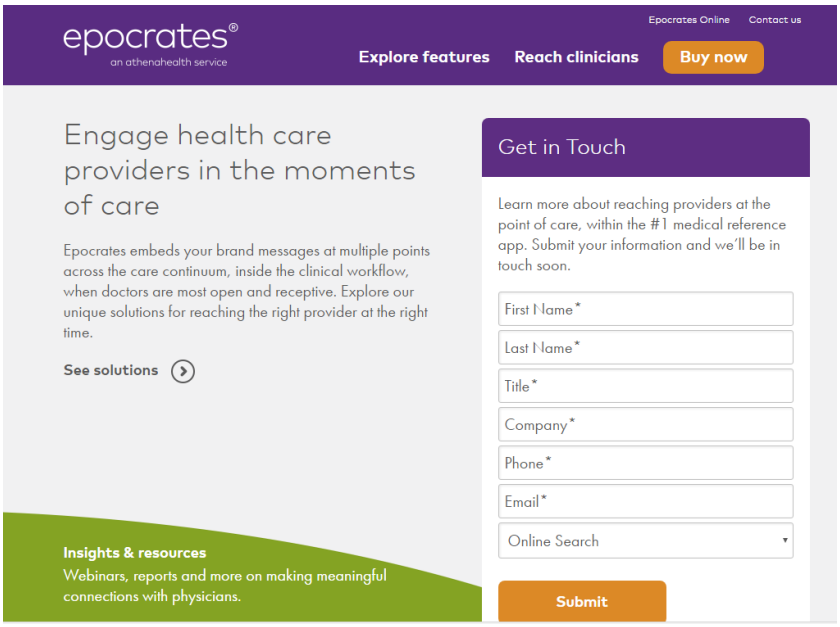


Figure 5.17 – Example of a physician portal – Epocrates.com

Source: Epocrates (2017)

A third type of healthcare portal is sales portals, which transfer sales processes to the internet. As noted by Puschmann & Alt (2001), these include on-line pharmacies, and these can be business-to-business, or business-to-consumer.

The fourth type is integration portals, as noted by Puschmann & Alt (2001), incorporate a series of stakeholders who are in constant interaction among themselves, such as healthcare institutions, payers (insurance companies), and other, allowing integration at three levels: clinical (physicians, pharmaceutical companies, pharmacies and insurance companies), administrative (hospitals, physicians, manufacturers of medical devices, pharmaceutical companies), and financial (insurance companies, physicians, hospitals and pharmacies). An example of integration portal is shown below, in figure 5.18.

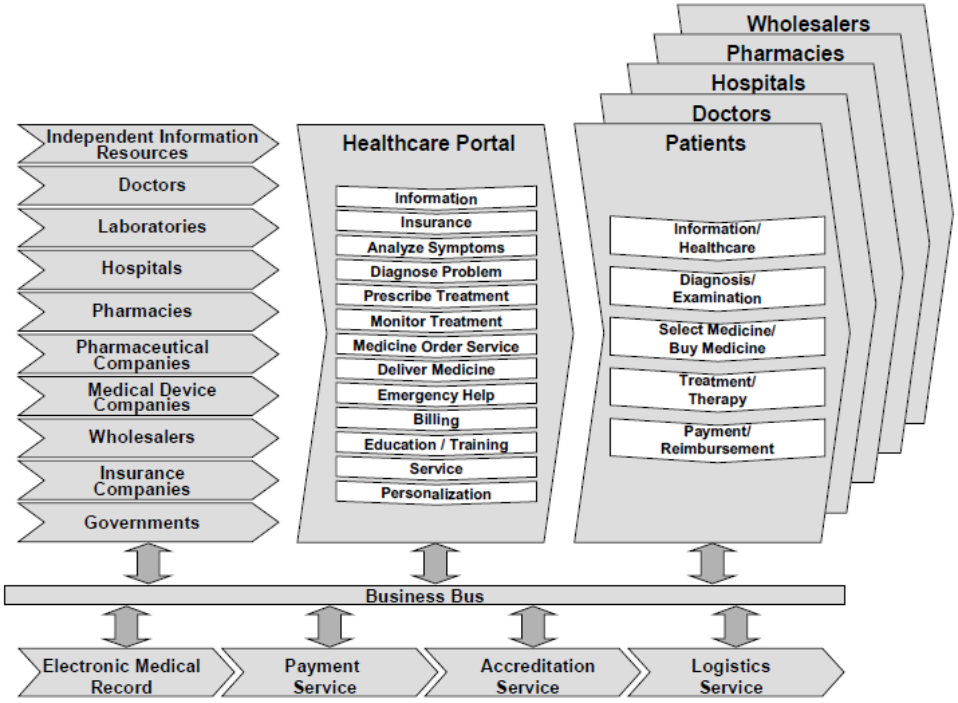


Figure 5.18 – Architecture of a healthcare integration portal

Source: Puschmann & Alt (2001)

Healthcare portals can provide pharmaceutical companies advertising services directed at prescribers, and in the case of integrated portals may also allow for advertising and campaign management directed at pharmacies.

5.6.4. Health social networks

A health social network is «*a website where consumers may be able to find health resources at a number of different levels (…). Services may range from a basic tier of emotional support and information sharing to Q&A with physicians to quantified self-tracking to clinical trials access*» (p. 495), definition proposed by Swan (2009). She also noted that these social networks can be targeted not only to patients, but also to caretakers, researchers and other interested parties.

Domingo (2010) also underlined that healthcare social networks can be either physician or patient oriented. She explained that while physician social networks allow doctors to share clinical cases, videos, images, and medical know-how, patient social networks put emphasis on direct patient support and disease awareness, providing information on health behaviors.

Examples of patient health social networks include, as referred by Swan (2009), PatientsLikeMe (www.patientslikeme.com) and Dailystrenght (www.dailystrenght.org), networks allowing patients to find other patients in comparable situations, exchanging information about their pathologies, whereas physician social networks examples include Sermo (www.sermo.com) and Medscape (www.medscape.com).

Pharmaceutical companies may benefit from these networks in more than one way. For instance, Sermo offers «*high impact banner ads with persistent targeted presence throughout the campaign with guaranteed 100% share of voice to support key brand objectives*» (Sermo, 2017), allowing companies to impact physicians during in a specified period of time. Even if some networks do not allow for direct promotion of drugs to patients or physicians, pharmaceutical companies can still benefit from developing for-profit partnerships. An example regarding PatientsLikeMe is data sharing with pharmaceutical and medical device companies to use data from permission-based access to patients, to provide these companies insights to improve treatment development and usage (Sarasohn-Kahn, 2008). An example regarding the way pharmaceutical companies can use platforms like Sermo was addressed by Barlas (2010). He explained that a company can monitor the conversations physicians develop in the platform, and when relevant topics emerge, the company can engage web-based activity. He also referred a Pfizer and Sermo joint-developed tool that allows Pfizer to interact with doctors who request information from Pfizer, for instance medical inquiries, which are scientifically answered by Pfizer medical department.

5.6.5. E-mailing (e-mail marketing)

In the pharmaceutical marketing scope, e-mailing consists of the use of physicians' e-mails to disseminate information about medicines, including promotional and scientific information. E-mailing is a non-personal channel, as addressed in ZS Affinity Monitor 2014 executive summary (ZS, 2014b). It is also known as e-mail marketing, as a promotion tool aimed at physicians (Pedroso & Nakano, 2009).

There are two basic ways pharmaceutical companies can use to reach physicians by e-mail. One is using their own customer information databases, which can be populated with information regarding the physicians they interact with. E-mail accounts are then used in order to contact physicians. Another is using third part service providers such as healthcare portals such as Simposium in Portugal, or CRM systems providers such as IQVIA globally.

As explained before, pharmaceutical companies can target physician groups with specific contents.

IMS Health (2016), in its ChannelDynamics Global Reference 2016 edition, evidenced that the global investment of pharmaceutical companies in e-mailing reached USD$963 million in 2015, a growth of 46,5% when compared with 2014. In terms of the weight on digital channels (measured by IMS Health as the sum of e-meetings, e-mailing and e-detailing), e-mailing relative magnitude increased from 29,1% in 2014 to 37% in 2015.

5.6.6. e-Continuing medical education (e-CME)

Continuing medical education (CME) can also be one of the available promotion tools pharmaceutical companies may use to interact with physicians using digital communication channels. Wutoh, Boren & Balas (2004) reviewed the impact of internet-based CME interventions on physician performance and health care outcomes, finding that these internet-based programs were equally effective to traditional formats of CME in communicating knowledge. In their review, they noted that on-line CME (or e-CME) may include several channels such as e-mail, and the internet.

Webinars are also one type of e-CME. According to Buxton, Burns & De Muth (2012), webinars are «*presentations, lectures, workshops, or seminars transmitted over the World Wide Web and are usually live and interactive*» (p. 2), and usually include chat tools where the health care professional has the ability to ask questions and receive answers in real time. Buxton, Burns & De Muth (2012) noted that while webinars are typically live, Web casts are presentations that are viewed online, but previously prerecorded.

5.6.7. e-Direct-to-consumer advertising and Web 2.0

Web 2.0 is the network as platform, spanning all connected devices (o'Reilly, 2005). This evolution from passive or static content (Web 1.0), to dynamic content shared by users to develop new on-line services (web. 2.0). The spectrum of social networking tools used by drug companies is as broad as those available and can include Facebook pages, Twitter accounts, blogs or RSS feeds, dedicated YouTube channels, and Apple iTunes applications sponsored by drug companies. These tools and applications are accessible globally, despite the fact the DTCA in prescription drugs is only permitted in two countries in the world (USA and New Zealand), as highlighted by Liang & Mackey (2011). Southwell & Rupert (2016) underlined that the global reach of these tools poses challenges to the FDA, to the European

Medicines Agency (EMA) and other agencies, regarding on-line promotion of prescription drugs.

In their research on the prevalence and health implications of social media in DTCA, Liang & Mackey (2011) found that all 10 pharmaceutical companies selected to their panel had a presence of DTCA 2.0 (DTCA in the scope of Web 2.0), including Facebook, Twitter, sponsored blogs, and really simple syndication (RSS) feeds. Eight companies had youtube channels, and eight had mobile applications to health care communication. Considering the drugs perimeter selected by the researchers, nine out of ten had dedicated websites, eight had Facebook pages, nine had Twitter activity, and eight had DTCA on youtube. These conclusions evidence the substantially high prevalence of DTCA in on-line media. The implications for the pharmaceutical companies are clear: it is an additional tool for communicating and interacting with patients and health care professionals. The full extent of Web 2.0 philosophy can however only be implemented in countries where DTCA is allowed (the USA and New Zealand, as addressed before). It also requires sponsorship identification, so that patients can know the online sources of information, including financial funding, noted Liang & Mackey (2011). This is a sensitive theme, which was studied by DeAndrea & Vendemia (2016), whose research suggested that the disclosure of pharmaceutical companies' affiliations and control of user-generated comments may affect how on-line users evaluate drug information, and also their behavior in terms of information dissemination using on and offline social networks, thus justifying the concern about these issues.

Southwell & Rupert (2016) also addressed the online possibilities companies have to promote their prescription drugs. They highlighted several tools such as video testimonials, printable coupons, and hyperlinks to disease information or medical resources.

These tools can not only be managed directly (using their own resources, websites and applications), but also indirectly (sponsoring third parties) by pharmaceutical companies. Sponsorship of blogs covering health related issues can allow pharmaceutical companies institutional promotion and support to specific pathologies. For instance, the blog Healthline (www.healthline.com) accepts sponsorships from pharmaceutical companies that fit with the mission and vision of the website (Sarasohn-Kahn, 2008).

Search engine optimization, where search ranks are influenced by a search engine so that a certain result can appear more often is also an effective tool pharmaceutical companies can use, as noted by Parekh, Kapupara & Shah (2016) in their review of digital pharmaceutical

marketing. Also, they highlighted that search engines use social media activity for marketing purposes, aiding the promoted product position on search engine results pages, allowing a direct connection of the company with its consumers.

5.6.8. Sub-chapter synthesis of main findings

This chapter covered promotion tools using digital communication channels, utilized by pharmaceutical manufacturers to promote their prescription medicines to physicians. These tools – which are still marginal worldwide in terms of investment magnitude - include e-detailing, e-sampling, company websites and healthcare portals, health social networks, e-mailing, online continuing medical education (e-CME), and e-Direct-to-consumer advertising, in the scope of Web 2.0.

There are two forms of e-detailing: virtual (interactive) e-detailing, also known by self-detailing, and video (live) e-detailing. E-detailing has been growing its penetration as a promotion tool, given some reasons: increased physician use of the internet, increased opportunity costs of physicians, and fear of pharmaceutical manufacturers to lose the digital presence. E-detailing can bring several benefits to both physicians (including convenience, additional information) and to manufacturers (complementing traditional detailing, reaching out-of-target physicians, in a cost-effective manner). E-detailing has been shown to positively impact prescriptions of the promoted drugs, when combined with traditional detailing.

E-sampling allows physicians to request drug samples through a website or a health care portal and contributes to increase the knowledge manufacturers have about drug sample requesters. Pharmaceutical manufacturers can also use company websites and health care portals to connect several players, providing adequate services, content and applications, but also advertising services impacting physicians and pharmacies. Physician-oriented health social networks can offer manufacturers the ability to post high impact banner ads targeted to specific physicians. E-mailing (or e-mail marketing) allows manufacturers to send targeted content to specific physician audiences. On-line continuing medical education can be used by pharmaceutical manufacturers to interact with physicians in the scope of training and education, through internet-based programs (including webinars and web casts). Pharmaceutical manufacturers can also take advantage of the Web 2.0 approach to interact with patients by using search engine optimization, sponsored blogs, and social media (e-Direct-to-consumer advertising).

5.7.Investment magnitude

Manufacturers investments are typically monitored by companies such as IMS Health, which aggregates them in categories including detailing, samples, meetings, advertising, clinical trials, direct to consumer marketing (DTC), mailing and digital (IMS Health, 2015a). The most important instrument is detailing, reaching 62,5% of the total investment. The second most important instrument according to IMS Health (2015a) is samples (11,1%), and then followed by meetings (11,1%) and DTC (6,5%). The digital channel reaches only 3,2% of the total investment but evidences a growth of 32,2% over the previous year.

According to Gagnon & Lexchin (2008), the total pharmaceutical industry promotion spent to impact medical practitioners reached US$57,5 billion in 2004 in the United States, of which US$20,4 billion on detailing and US$15,9 billion on samples, meaning that detailing is the promotion tool with the highest total investment, used by pharmaceutical companies to interact with physicians. Yi, Anandalingamb & Sorrell (2003) had already noted that pharmaceutical manufacturers' biggest investment is on their sales force (detailing activities). More recently, Datta & Dave (2016) also underlined that «*most of (83%) of Rx promotion is directed at physicians in the form of visits by pharmaceutical representatives (known as detailing))*» (p. 1). Gagnon & Lexchin (2008) compiled data from independent private market research agencies, pharmaceutical companies and other sources -, these investments represent US$61.000 in promotion per physician. When divided by the US domestic sales of US$235,4 billion, pharmaceutical industry promotion reaches a percentage of 24,4%, almost twice as R&D which represents 13,4% of domestic sales. As reported by IMS Health (2015a) on its Global Pharmaceuticals Marketing Channel Reference report, the worldwide pharmaceutical industry promotion investment in sales force and marketing channels reached almost US$71 billion in constant US dollars, dropping by -1,4% from 2013.

Physicians are the main targets of pharmaceutical marketing teams (Salmasi et al, 2016), as they are the main prescribers. A study conducted by Cegedim Strategic Data revealed that the top 20 pharmaceutical companies' promotion investment on professional detailing was five times the investment on DTCA (82% vs 18% weight), in 2013 (Cegedim, 2014). IMS Health (2015a) data also suggests physicians are, by far, the main targets of pharmaceutical industry promotion, as only 6,5% of the total investment is allocated to DTCA.

5.8.Additional perspectives on pharmaceutical promotion

In this sub-chapter, we will address additional perspectives regarding pharmaceutical promotion tools. The first addresses stakeholders' perspectives on detailing activities to physicians, proving a perspective from pharmaceutical manufacturers, physicians, pharmaceutical sales representatives, nurses, pharmacists and patients. The second will address multichannel marketing, or the use of several marketing channels by pharmaceutical companies, aimed at creating and maintaining interactions with physicians. It then will approach push and pull promotion approaches in the pharmaceutical industry using not only traditional but also digital communication channels, physicians' preference on digital channels, physicians' prescription attitude on digital channels, evaluation of the effectiveness of the promotion activities, ending with a discussion of the main ethical issues raised when addressing pharmaceutical industry promotion directed at prescribers.

5.8.1. Stakeholders' perceptions

Manufacturers

The pharmaceutical industry is a major player in healthcare management. The last European Federation of Pharmaceutical Industries and Associations report for the year 2015 (EFPIA, 2016c) estimates that this industry employs more than 723 thousand people in Europe (eight thousand in Portugal) and generates three to four times more employment indirectly – upstream and downstream, investing more than €30 thousand million in research and investment, ranking second on the top industrial sectors by overall R&D intensity in 2016 (EU R&D Scoreboard, 2016). The cost of developing a new drug (including the cost of failures) reaches an average of US $2.588 million (DiMasi, Grabowski & Hansen, 2016), and by the time a drug reaches the market, an average of 12–13 years will have passed since the first synthesis of the new active substance (EFPIA, 2016c).

The health expenditure (current expenditure on health, as a percentage of the gross domestic product) reached an average of 9,0% in 2014, in OECD countries (OECD, 2016a). As a comparison between some countries, in the US reached 16,9%, in the UK 9,8%, in Germany 11,1%, in France 11,0%, in Portugal 8,9%, in Spain 9,0%, in Italy 9,1%, and Greece 8,2%. The other proportion of health expenditure costs relates to outpatient care & others, and in-patient care (hospital).

But what is the real weight of the pharmaceuticals in the GDP? Current expenditure on pharmaceuticals (prescribed and over-the-counter medicines) and other medical non-durables,

as a percentage of current expenditure on health, reached an average of 16,3% in OECD countries (OECD, 2016a). The US reached a proportion of 12,3%, the UK 12,2%, Germany 14,5%, France 15,0%, Portugal 15,4%, Spain 17,9%, Italy 17,0%, and Greece 28,4%. This means that, for the OECD countries, the average proportion of GDP allocated to pharmaceuticals is 1,5% (US 2,1%, UK 1,2%, Germany 1,6%, France 1,7%, Portugal 1,4%, Spain 1,6%, Italy 1,5%, and Greece 2,3%).

PhRMA, the Pharmaceutical Research and Manufacturers of America, issued a report in 2008 called Pharmaceutical Marketing in Perspective, where it defended the pharmaceutical perspective on pharmaceutical marketing. One of the main arguments written consists of the value it provides to physicians by providing FDA-regulated educational and scientific information about new drugs. In order to preempt some arguing about the possible pharmaceutical marketing impact on the prescriptions of new medicines, PhRMA states, based on a survey requested to KRC Research, that marketing is only one factor considered by physicians in the moment of choosing a drug, since physicians' judgement and experiences, as well as other sources of information, also impact the drug choice. KRC Research was commissioned again by PhRMA in 2011, and the report highlighted that physicians classified information from pharmaceutical company representatives and pharmaceutical company-sponsored education programs featuring physician speakers (not CME) in 12th and 13th places out of a list of 15 possible factors that physicians consider when prescribing (KRC Research, 2011). In the same report, 92% of physicians considered the information provided by pharmaceutical company representatives as useful (32% strongly agree + 60% somewhat agree), and 84% considered the information received as reliable (27% strongly agree + 57% somewhat agree).

PhRMA (2008) also states that pharmaceutical marketing «*plays an important role in providing information about brand medicines and helps balance other factors that emphasize promoting older treatments and that reduce use of needed medicines*». An article from Manchanda & Honka (2005) underlined the importance of detailing as an important information source for physicians. PhRMA (2008) suggests that, without pharmaceutical marketing, health care professionals would be «*less likely to have the latest, accurate information available regarding prescription medicines, which play an increasing role in effective health care*», enabling pharmaceutical research companies to «*inform health care professionals about the benefits and risks of their products, provide scientific and educational information about their use, and obtain information and advice about their medicines through*

consultation with medical experts». PhRMA (2008) also stresses the investment pharmaceutical companies make by developing marketing activities aimed at bringing new information about new treatments into the health care system, defending that «*even many years after new types of medicines are introduced, a large share of patients who should be using them according to clinical practice guidelines go untreated. In fact, these treatment gaps are often viewed as serious public health problems that lead to poor patient outcomes and high health costs—both human and economic—that could have been avoided*».

PhRMA presents another strong argument: the fact that public and private payers (such as insurers) strongly influence which medicines patients will receive. EFPIA (2016c) refers, in its report The Pharmaceutical Industry in Figures – Key Data 2016, the pharmaceutical industry contribution to the increase in life expectancy. Research conducted by Lichtenberg (2014a) was in the base of this argument, whose findings suggest that 1,74 years of additional mean life expectancy at birth were gained from 2000 to 2009, across 30 OECD countries, and 73% of this improvement was generated by innovative medicines (with other factors taken into account such as education, income, immunization, health system access and reduction of risk factors). In another research, Lichtenberg (2014b) analyzed the impact of pharmaceutical innovation in the US mean number of work loss days, school loss days, and hospital admissions, finding that there was a more rapid decline, on those indicators, among medical conditions that increased the use of new post-1990 drugs. Another conclusion was that pharmaceutical innovation impact on the reduction in work loss days and hospital admissions is estimated to be three fold the cost of the new drugs consumed by patients.

A recent article from Jacob (2018) discussed the legitimacy of the pharmaceutical industry to promote the drugs they develop. He noted that the industry argument to continue the promotion efforts is simple, where the lack of promotion would lead to lower drug sales and profits, which would imply a reduction in R&D, and which ultimately would negatively impact the drug discovery and development outcomes.

All these arguments, from the research and development risks and costs, to the benefits given to health care practitioners, patients and society, seem to be intended to demonstrate the pharmaceutical industry legitimacy to engage in marketing activities, mainly directed at prescribers.

Physicians

This topic will address physicians' perceptions on the interactions developed between them and PSRs. Both positive and negative perceptions can be found in research conducted involving physicians on their opinion about PSRs promotion activities.

- **Positive perceptions**

According to research conducted by Andaleeb and Tallman (1996), using a structured-undisguised questionnaire to inquiry a sample of 95 physicians, physicians see the PSR «*as an important source of information, yet they feel they could get the needed information without the PSR's assistance*» (p. 87). They also argued that «*physicians had friendly relations with the PSRs and did not distrust them, yet they did not view them as a vital part of their practice*» (p. 87). Prosser & Walley (2003b) developed a qualitative study where they found that general practitioners consider that pharmaceutical representatives bring them new drug information promptly, bringing convenience and accessibility to their practice. Cegedim (2011) developed a report consisting of results from a panel of 5,6 million product detailing mentions in 30 countries, showing that 93,8% of physicians (both general practitioners and specialists) classified sales representative calls as useful and of value to their professional practice.

Spiller & Wymer (2001) studied the importance given by physicians to different promotional tactics used by the pharmaceutical industry. Using a sample of 109 physicians attending a medical conference, they found that the highest levels of usefulness to physicians were medical books (with a category mean of 3,7 out of 4), medical journals (3,4), symposia / conferences (3,4), free samples (3,2), other physicians (3,1), PSRs (2,8) and pharmaceutical brochures / ads (2,7).

As reported by Prosser & Walley (2003b), several physicians commented that they retained information better when it was communicated verbally by PSRs, which attributes an important role to the face to face characteristic of detailing. Using qualitative research through focus groups, Chimonas, Brennan & Rothman (2007) found that physicians maintained favorable views of exchanges kept with PSR through detailing, and presented some excerpts of the transcriptions of the group dynamics: «*they just tell you about their product and you learn about it. A lot of the things I know about the new drugs, I learned from the pharmaceutical representatives*» (p. 187). Anderson, Silverman & Loewenstein (2009) developed research addressing factors associated with physicians' reliance on pharmaceutical

sales representatives. They found that more than three fourths of the physicians consider PSRs' information as at least somewhat valuable. They also found that almost three out of ten physicians allege using PSRs often or almost always in the scope of the prescription of a new drug, and 44% use PSRs sometimes.

Regarding gifts provided by PSRs, physicians tend to consider educational gifts higher in terms of appropriateness, compared to recreational gifts given by the pharmaceutical industry (Brett, Burr & Moloo, 2003). Drug samples are usually well accepted as highlighted by Salmasi et al (2016). These researchers found that «*physicians generally see meetings with pharmaceutical representatives as advantageous to everyone: the patients, because they receive free drug samples, the hospital/clinic, because they would receive stationery, books, and most important, themselves, as these meetings help they stay up-to-date and aware of newly launched medications*» (p. 11).

- **Negative perceptions**

PSRs may provoke some time pressure on some physicians' agendas, as noted by Prosser & Walley (2003b). They also found that some physicians had objections regarding PSRs' behaviors, including alleged «*commercially-biased information, representatives' confrontational and argumentative approach, and a lack of legitimacy as information providers and thus subsequent undue influence on prescribing*» (p. 309).

Manchanda & Chintagunta (2004) found that, over a certain level of detailing pressure, some physicians (approximately 15%) may reduce their prescriptions of the over-detailed drug. This evidence may suggest that PSRs activities, at this extremely high magnitude, may be perceived negatively by physicians, given their opportunity cost of time.

- **Perception of immunity against promotion initiatives**

Prosser & Walley (2003b) highlighted that «*although findings suggest that GPs were highly aware that representatives could influence prescribing, in the main they did not attribute negative influence to their own prescribing*» (p. 310). This is consistent with quantitative research conducted by Steinman, Shlipak & McPhee (2001), where more than 60% of the physicians stated that pharmaceutical industry promotions and contacts did not have influence on their own prescribing, while only 16% believed other physicians were unaffected. Riese et al (2015) also found similar evidence among trainees, as they were more likely to believe that pharmaceutical industry interactions have no impact on their own prescribing behavior, versus

the prescribing behavior of other physicians. This pattern is also underlined by Salmasi et al (2016) in their review, as a certain perception of immunity against pharmaceutical companies' promotion initiatives.

Pharmaceutical sales representatives

Malhotra, Kondal, Shafiq, Sidhu & Pandhi (2004) concluded, after deploying a research to study pharmaceutical sales representatives' perceptions of factors inducing prescription writing, that an important number of representatives believed they had a considerable influence on physicians' prescription patterns (impacting more than 50% of their prescriptions). This result is contrary to physicians' perceptions of representatives' influence on their prescriptions, as seen in Steinman et al (2001). However, Malhotra et al (2004) also find that representatives elect the provision of scientific information to physicians as the most effective sales promotion. Parker & Pettijohn (2006) developed research comparing physicians and PSRs differences in perceptions regarding a battery of 23 parallel questions that were answered by both stakeholders' types. When evaluating the effect of push promotion, PSRs were much more confident on the impact of their promotion activities in the prescription likelihood of drug categories promoted, compared to physicians' answers (statistically significant differences, p=0,02). Interestingly, PSRs were also much more confident in the value of their activities in providing enough information for a drug prescription, than physicians (average of 3,7 vs 2,6, using a Likert scale of 1 (strongly disagree) to 5 (strongly agree)). The 2,6 average of physicians' answers to this last point may suggest that the information provided by PSRs may not be considered as sufficient, in the scope of a prescription decision. It appears that PSRs seem to consider their influence on physicians higher than the declared influence recognized by the physicians in relation to the formers' activities.

Malhotra et al (2004) also evidenced that representatives consider the communication skills as the most important attribute in drug promotion, and that younger physicians might be more easily influenced than physicians with more experience. Regarding representatives' perceptions about physicians' attitudes in relation to gifts, more than 30% of representatives alleged that physicians actively take initiative to ask for gifts in return for writing a prescription.

Non-prescribing clinicians

- **Nurses**

In some countries, such as the US and Australia, some nurses and physician assistants have the statutory authority to prescribe drugs, according to Ladd & Hoyt (2016). Pharmaceutical industry has been targeting nurses for a long time (Ladd, Mahoney & Emani, 2010). This targeting directed at nurses may seem counter-intuitive, as most of the nurses do not have the authority to prescribe drugs. However, as highlighted by Jutel & Menkes (2010) after addressing a sample of 100 senior registered nurses (of which only 2% had prescription rights), four out of five (79%) nurses reported recommending treatments to physicians and providing advice to patients about OTC medications; three out of four (77%) nurses reported that they have participated in the development of guidelines or policies including the use of medications. In the same research, all (100%) surveyed nurses reported that they can influence prescriptions of drugs in one way or another.

Ladd et al (2010) found, after studying results of a sample of 263 nurses, that more than 19 out 20 nurses (96%) reported having regular contact with pharmaceutical sales representatives. Regarding the reliability of the received information from the pharmaceutical industry, four out of five nurses (83%) considered it reliable and more than nine out of ten nurses (93%) received free gifts given by the sales representatives, but stated it had no effect on the probability to prescribe the emphasized drug. Ladd et al (2010) also found that almost six out of ten nurses (59%) reported regular attendance at pharmaceutical industry sponsored lunch events (one to five times in the previous six months), and almost two thirds (64%) reported regular attendance at dinner events during the same period. Almost all (96%) nurses had attended continuing education programs over the past 5 years. 78% of the respondents considered meal events as a good-to-excellent way to receive information about a new drug, and 69% considered those events encourage the use of those new drugs. Approximately half (48%) of respondents stated that they were more likely to prescribe a new drug, after attending to an industry-sponsored event. Regarding ethical issues related to the relation of the pharmaceutical industry and nurses, six out of ten nurses (61%) stated that the practice of providing small gifts and meals to clinical offices by the pharmaceutical industry was acceptable.

Grundy, Bero & Malone (2016) developed a qualitative study which suggested nurses had a relevant interaction with the pharmaceutical industry. In their study, the researchers found that

all interviewed nurses (56) reported interactions with the industry in the previous year, including face to face meetings, on an average of 13 times in the same period. The forms of interaction similarly included industry-sponsored lunches, dinners or events (39 out of 56), offers of gifts (40 out of 56) or product samples (34 out of 56). 15 out of 56 nurses declared having received paid travel. The interactions seemed to be more frequent with medical devices industry (47 out of 56), but also with the pharmaceutical industry (31 out of 56).

In another study, Grundy, Fabbri, Mintzes, Swandari & Bero (2016b) have demonstrated that four out of ten (39,4%) nurse practitioners in Australia were present at a subset of industry-sponsored events, twice as much as primary care physicians (21.1%). The researchers also found that nurses were present at 35% of all events that included healthcare practitioners from several disciplines (physicians, nurses, and other).

Previous research conducted by Crigger, Barnes, Junko, Rahal & Sheek (2009) had already highlighted the relation between pharmaceutical industry and nurses. They found that the majority of nurses who answered to their questionnaire frequently receive samples, office supplies, equipment and educational items. A great majority of nurses considered that industry-sponsored lunches and dinners, as well as sponsored trips to educational programs are ethical. The authors also found that nurses who responded to the survey perceived themselves as less influenced by the pharmaceutical industry, than other nurses. Despite the differences in scope, this finding is consistent with the ones highlighted by Steinman et al (2001), Riese et al (2015) and Salmasi et al (2016), regarding physicians.

Jutel & Menkes (2009) also found that almost two out of three (65%) nurses had contact with pharmaceutical sales representatives, three out of four (75%) had accepted gifts from these representatives, and two thirds (67%) declared they believed information coming from the pharmaceutical industry improved their practice. In the same research, one out of three (35%) nurses thought it is ethically acceptable to receive gifts and sponsorship.

- **Pharmacists**

Pharmacists too have been targeted by pharmaceutical industry marketing. Farthing-Papineau & Peak (2005) conducted a survey on pharmacists' perception of the pharmaceutical industry and found that half of the surveyed pharmacists had a positive image about the pharmaceutical industry, one quarter had a neutral image, and one quarter had a negative image. Saavedra, O'Connor & Fugh-Berman (2017), in their qualitative research, documented that all interviewed pharmacists reported having had interactions with pharmaceutical

company representatives. While the interviewed pharmacists recognized physicians as the main targets for pharmaceutical marketing, most have been given free resources or services from industry, such as educational courses. As underlined by Saavedra et al (2017), «*expanding roles for pharmacists may make them even more attractive targets for future industry attention*» (p. 1). Some pharmaceutical companies are using alternative communication channels to impact pharmacists, such as telemarketing. For instance, IQVIA and 2Logical have been offering telemarketing services to pharmaceutical companies in Portugal, aimed at promoting specific products and promotions to pharmacies.

Pharmacists have the ability to dispense drugs prescribed by physicians and recommend OTC medications to patients and in some cases can change the generics brand prescribed by the physicians (as seen in Portugal, in some situations). Saavedra et al (2017) noted that one pharmacist stated that pharmacists practicing at rural areas may have much more influence on physicians. Another interviewee stated that pharmacists can make recommendations to physicians based on what the pharmacist know about the patient.

The results from the referred authors underline the fact that physicians are not the only professionals being target by pharmaceutical industry marketing.

Patients

As underlined by Gönül et al (2001), patients are the users and payers of medical products and services by excellence, so their role seems to be limited regarding the choice of the drug prescribed. Being at the end of the buying decision process, it is relevant to study patients' awareness and perceptions about pharmaceutical industry relation with physicians, especially about gifts. Mainous, Hueston & Rich (1995), in a survey deployed on patients, demonstrated that 82% of the respondents were aware that physicians received office-use gifts, and only 32% were aware that physicians received personal gifts. In the same research, patients' attitude toward personal gifts given by the pharmaceutical industry to physicians was more critical than toward office-use gifts, having a perceived negative effect both on healthcare cost (42% vs 26% of respondents) and quality (23% vs 13%).

More than 10 years later, Jastifer & Roberts (2009) surveyed patients on similar questions, regarding awareness and attitudes in relation to gifts given by sales reps to physicians. The researchers found relatively high levels of patient awareness of gifts such as drug samples (93,9% of respondents) and ballpoint pens (76,2%). However, the awareness of other gifts such as dinner out (36,6%), spouse meal and dinner out (23,1%) or golf tournament fees

(19%) was much lower. Approval rates varied immensely from 69,1% regarding drug samples and 54,2% regarding ballpoint pens, to 7,3% regarding spouse meal and dinner out and 3,7% regarding golf tournament fees. These results confirm, as underlined by the authors, a great majority of patients not approving most of the gifts, especially those with a higher perceived monetary value.

Green, Masters, James, Simmons & Lehman (2012), using a different methodological approach regarding data collection (survey to patients at clinics waiting rooms), also evidenced different patient awareness levels depending on the type of gifts, from 48% regarding patient education materials with drug company logos on them, to 7% regarding office staff eating lunches paid for by drug companies. Results from this research also show that almost six out of ten respondent patients (59%) would have less trust in their physician if they learned the physician had accepted gifts with a monetary value higher than $100 or went on pharmaceutical industry-sponsored trips (58%) or sporting events (54%).

Fadlallah et al (2016) highlight, in their review, that patients usually report lower awareness for personal gifts relative to office-use gifts, and that patients would more easily accept the fact of physicians receiving educational and office-use gifts, compared to receiving personal gifts. They also found an association between perceived relationships with the pharmaceutical industry and lower trust in physicians.

5.8.2. Push vs Pull

As addressed by Parker & Pettijohn (2006), the pharmaceutical industry constitutes a very good example of an industry combining combines both push and pull strategies in their promotional efforts. They explained that while push strategies rely «*primarily on personal selling and sales promotion as a means to "push" a product through the marketing channel*» (p. 28), pull strategies «*rely on advertising and sales promotion to the end user to "pull" the product through the marketing channels*» (p. 28). Here the end user is the patient, in the scope of DTCA, promotional activity allowed in the USA and in New Zealand. Parker & Pettijohn (2006) also explained that when pharmaceutical companies combine both push and pull strategies, having as a goal increases in product awareness and prescriptions.

Wieringa & Leeflang (2013) explained that direc-to-consumer advertising constitutes the "pull" effect, and detailing, medical journal advertising and physician meetings constitute the "push" effect. Ruiz-Conde, Wieringa & Leeflang (2014) explained that the «*push marketing*

strategy, which targeted mainly the physicians, includes physician meetings and seminars, medical journal advertising, samples, direct mail, and detailing» (p. 51).

In the scope of direct to physician promotion, pull strategy concept also applies. Puschmann & Alt (2001) explained that the traditional sales organization in the pharmaceutical industry has been based in a cost-intensive push strategy, but a shift to a pull strategy may increase efficiency, where doctors will more and more search and satisfy their information needs via on-line sources such as healthcare portals. Digital communication channels have allowed pharmaceutical companies to direct pull promotion strategies to physicians, who actively search, on their own choice, for contents through several promotion tools. One example is e-sampling, where doctors can apply for samples in a request form, using a laptop or mobile devices (Kumar & Panigrahi, 2014). Another example is self-detailing, a form of e-detailing, where doctors receive an interactive multimedia experience training for a product, and can then, on their initiative, request additional information, apply for samples, or ask for a face-to-face visit with a PSR (Heutschi et al, 2003). Pull strategy can also be seen in physicians' search for drug-related information in pharmaceutical companies websites or health information portals, as addressed previously.

Bernewitz (2001) addressed the several push (contact initiative starting from the pharmaceutical company) and pull (contact initiative starting from the physician) promotion tools available to pharmaceutical companies in their interaction with doctors, combining them into a chart with one axis as personal interaction, and another axis as control of information flow, seen below in figure 5.19. Most pull promotion tools appear at the upper right quadrant of the chart, involving a lower level of personal interaction.

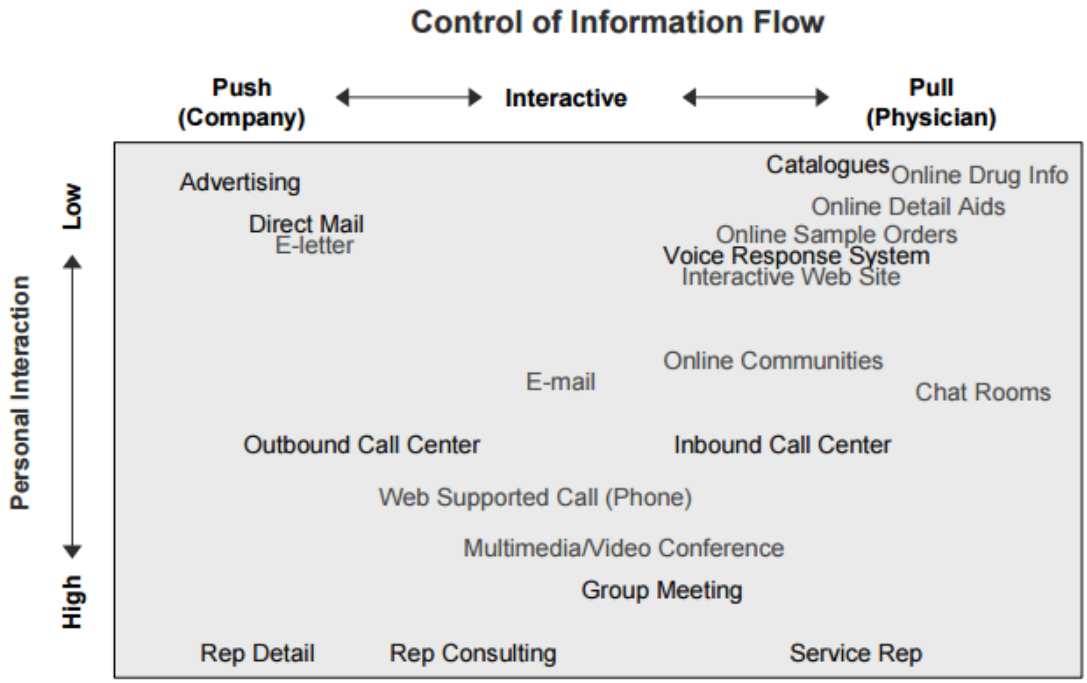


Figure 5.19 – Pharmaceutical companies' spectrum of communication options

Source: Bernewitz (2001)

5.8.3. Physicians preference on digital channels

QuintilesIMS, on its Channel preference versus promotion reality white paper, surveyed physicians from 35 countries addressing them on which channels were more preferred, in the scope of their interactions with the pharmaceutical industry. QuintilesIMS (2016b) not only analyzed the stated preferences in terms of channels, but also the current reality of channel utilization by pharmaceutical companies (shown in figure 5.20). They found very diverse realities by country, and by physician specialty. For instance, in the USA, most of the specialties indicate a percentage of preference for digital channels in the 0% to 10% range, with however some very different results from diabetologists, cardiologists, rheumatologists, and infectious diseases specialists.

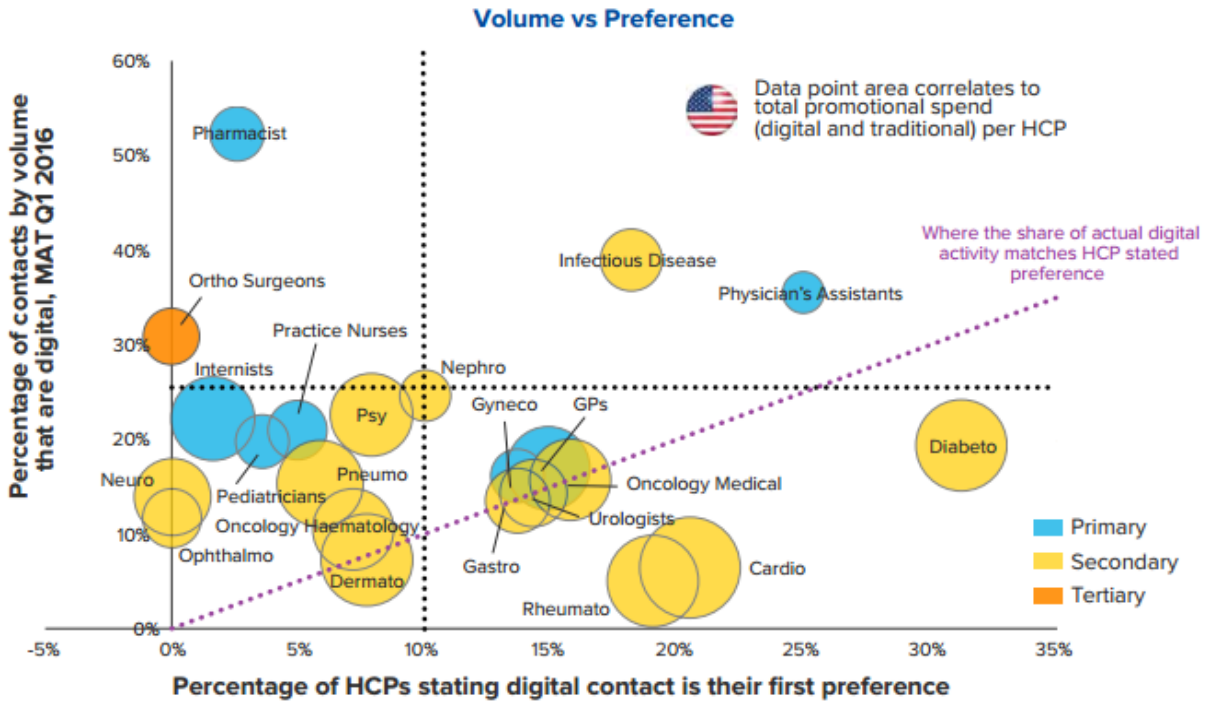


Figure 5.20 – Volume versus preference on digital channels – USA

Source: QuintilesIMS (2016b)

The results from the USA contrast with the ones from Japan, where the great majority of medical specialties are mainly impacted by digital channels, in a higher proportion than the one they stated as first preference for contact. Table 5.6 evidences the proportion of specialties receiving their preferred amount of digital activity. The UK and France appear to be more aligned in terms of what medical specialties want as digital meeting their activity preference.

Table 5.6 – Proportion of specialties receiving their preferred amount of digital activity

	Japan	USA	UK	France	Spain	Germany	Italy	China
Exceeds demand	94%	50%	17%	8%	0%	7%	0%	0%
Meets demand (within +/-10%)	6%	36%	61%	53%	24%	7%	0%	0%
Falls short of demand	0%	14%	22%	41%	76%	87%	100%	100%

Source: adapted from QuintilesIMS (2016b)

ZS Associates Affinity Monitor study (ZS, 2014) evidenced that while face to face channels still have the highest affinity, digital channels (both push and pull) already have high levels of affinity too. The study also showed that the percentage of doctors expressing favorable attitudes toward non-personal channels was substantially different within specialties. For

instance, Cardiologists were the specialty showing the highest percentage of unfavorableness regarding face to face interactions (11%), while only 16% expressed unfavorableness regarding non-personal promotion (the remaining 54% of physicians were PSR and non-personal promotion favorable). Conversely, 64% of dermatologist expressed unfavorableness regarding non-personal promotion interactions.

HealthLink Dimensions, a US company providing healthcare data solutions to healthcare and life science organizations, surveyed over 700 physicians and nurse practitioners to understand which practices they prefer in terms of communication. Their study found that 68% of physicians and nurses alleged preferring e-mail for initial contacts, while 11% want physical interactions such as direct mail or visits from PSRs (Healthlink, 2016).

A study conducted by Quantia and Capgemini Consulting in 2013, using a sample of almost three thousand physicians, addressing how physicians prefer to interact with pharmaceutical companies, evidenced some relevant results: one of the conclusions was that two thirds (67%) of physicians alleged they prefer digital access for pharmaceutical companies product information; another was that four out of ten physicians considers that digital media offers the most relevant and personalized content (Capgemini, 2013).

5.8.4. Physicians prescription attitude on digital channels

It is also relevant to understand whether physician prescription attitude will be impacted by the use of digital channels. Channel Dynamics, a regular study conducted by IMS Health, on physicians' declared intention to prescribe, highlighted that, for most of the countries analyzed, the relative impact of digital channels on prescription intention was lower than the impact of traditional channels. For instance, as seen in figure 5.21, in China physicians declared prescription intention was higher for digital than for traditional channels. France was at the lower end of the results, with less than half the relative impact of traditional channels.

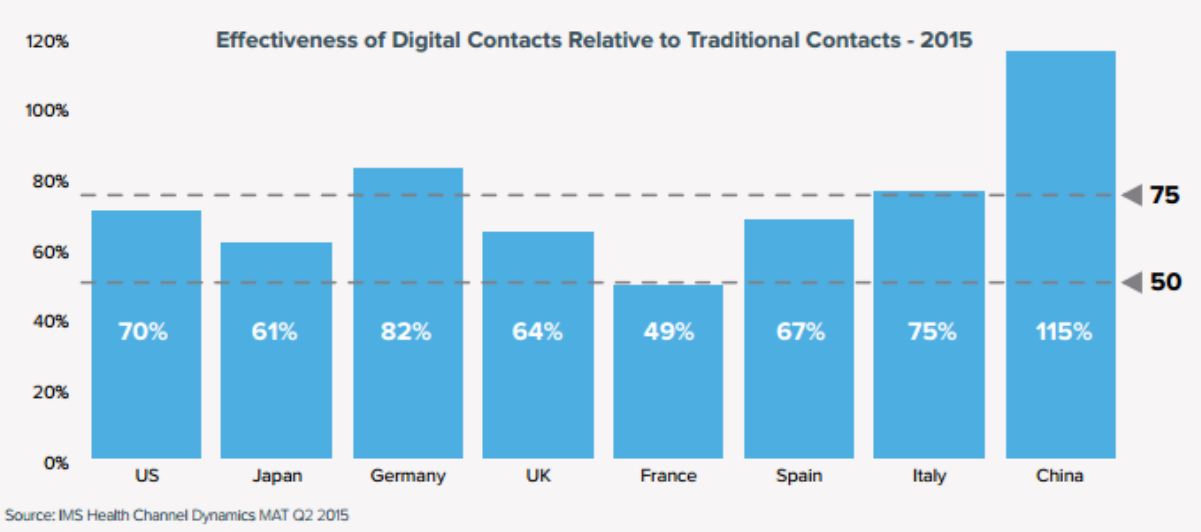


Figure 5.21 - Impact of digital contacts on intent to prescribe relative to traditional contacts

Source: IMS Health (2015b)

5.8.5. Comparative effectiveness of the promotion tools

Pharmaceutical companies make use of a series of tools to evaluate their promotion investments in terms of drug sales effectiveness. Manchanda, Rossi & Chintagunta (2004) highlighted that both academics and pharmaceutical industry practitioners develop sales response models in which sales measures are related to different levels of marketing mix variables. They demonstrated that, using physician level detailing response curves, detailing effectiveness can be improved in terms of additional drug sales generation (up to 12% higher volume), by optimizing the detailing intensity given each physician' responsiveness to this promotion instrument. This physician-level prescription information is available, as addressed later in this thesis, from companies like IMS Health (rebranded as IQVIA since the fourth quarter of 2017, after the merger with Quintiles), which purchase and compile prescription information records gathered through agreements with community pharmacies (Fugh-Berman & Ahari, 2007).

As covered by Stremersch & Van Dyck (2009), sales force management (where detailing is included) can be subject of decisions on optimal sales force sizing and targeting, decisions to optimize sales call quality, and the optimized use of drug samples, including sales response models such as the impact of detailing on prescription behavior. Sah & Fugh-Berman (2013) also underlined the fact that detailing – just as other promotional instruments – can be optimized so that pharmaceutical companies reach optimal levels in terms of cost versus

benefit. They referred that pharmaceutical companies develop response curves to study the marginal impact of different promotions on drugs sales, having as a goal the optimization of investments «*by targeting the right doctors with the right message at the right frequency through the right channel*» (p. 670), with a very high marketing sophisticated behavior.

In their research on physicians influence by the pharmaceutical industry, Sah & Fugh-Berman (2013) made a very interesting and pragmatic consideration about the interest of pharmaceutical companies in developing promotional activities targeting prescribers: «*Pharmaceutical companies and medical device manufacturers anticipate a return on their investment of billions of dollars on promotion. The effectiveness of specific marketing messages is calculated on the basis of uplifts in prescriptions or medical device sales from sales rep visits, gifts, meetings, continuing medical education seminars, and so on*» (p. 670).

To the extent of our knowledge, and based on the literature perimeter selected for analysis, no research is available comparing the effectiveness, on physicians' prescribing behavior, of a thorough set of promotion instruments using a time-series approach of prescriptions and promotion investments. There are however generalizations on the effectiveness of pharmaceutical promotional expenditures. An extremely relevant and useful article from Kremer, Bijmolt, Leeflang & Wieringa (2008) helped generate insights about the relative influence of promotion tools on drug sales. They performed a meta-analysis on the main pharmaceutical promotion instruments covered in the literature and found that detailing evidences the highest elasticities, followed by medical journal advertising, DTCA, and other direct-to-physician promotion tools such as meeting expenditures, direct mail, and drug samples. The average predicted elasticities they found are shown below in table 5.7.

Table 5.7 – Average predicted promotion elasticities - Kremer, Bijmolt, Leeflang & Wieringa (2008)

	Average predicted elasticity
Detailing (sales calls)	0,326
Medical journal advertising	0,123
DTCA	0,073
Other direct-to-physician	0,062

Source: Adapted from Kremer, Bijmolt, Leeflang & Wieringa (2008)

There is also research developed using time series, nonetheless comparing the effectiveness of a limited number of promotion instruments, adding to Kremer, Bijmolt, Leeflang & Wieringa (2008) previous research, by contributing with a higher granularity of promotion instruments, for instance including drug sampling, direct mail advertising, and e-detailing, however in a non-exhaustive manner. In the following pages, a series of previous research outcomes will be presented, to allow for additional insights on the relative magnitude of the effect of pharmaceutical promotion instruments, in their ability of influencing physician drug prescribing behavior.

Montgomery & Silk (1972) analyzed the effect, on prescription behavior, of three promotion instruments consisting of medical journal advertising, direct mailing, and samples and literature, and found significant and positive short and long-run elasticities for all three instruments. Table 5.8 below explicits the long-run elasticities.

Table 5.8 – Long-run elasticities - Montgomery & Silk (1972)

	Elasticities
Medical Journal advertising	0,365
Direct mailing	0,018
Samples and literature	0,108

Source: Adapted from Montgomery & Silk (1972)

Berndt, Bui, Reiley & Urban (1995) analyzed the factors affecting the growth of H2-antagonist drug market, and found that, among the promotion instruments, detailing had not only a positive impact on the number of prescriptions, but also it had the largest significant effects, higher than medical journal advertising and DTCA. Table 5.9 below evidences the elasticities found by Berndt, Bui, Reiley & Urban (1995).

Table 5.9 – Promotion tools elasticities - Berndt, Bui, Reiley & Urban (1995)

	Elasticities
Detailing	0,649
Medical Journal advertising	0,167
Direct-to-consumer advertising	0,052

Source: Adapted from Berndt, Bui, Reiley & Urban (1995)

Gönül et al (2001), when studying the effect of a series of variables to explain variations in physician prescription choices, found that detailing had a much stronger effect than drug sampling. The coefficients obtained are shown below in table 5.10.

Table 5.10 – Promotion tools regression coefficient estimates - Gönül et al (2001)

	Estimate
Detailing	0,1085
Drug sampling	0,0345

Source: adapted from Gönül et al (2001)

Narayanan, Manchanda & Chintagunta (2003), in their research of second-generation antihistamine brands, and using data from several promotion tools, found that detailing is relatively more impactful than other promotion activities, in terms of drugs prescriptions, discovering evidence for both informative and persuasive effects on physicians' prescription comportment. The instrument that ranked second in terms of impact on prescription behavior was a category composed by meetings, seminars and medical journal advertising, and in the third place were DTCA. The elasticities found by Narayanan, Manchanda & Chintagunta (2003) are shown below, in table 5.11.

Table 5.11 – Promotion tools elasticities - Narayanan, Manchanda & Chintagunta (2003)

	Elasticities		
	Allegra	Claritin	Zyrtec
Detailing	0,1143	0,0981	0,0978
Meetings and seminars + medical journal advertising	0,0519	0,0364	0,0453
Direct-to-consumer advertising	0,0147	0,0169	0,0137

Source: Adapted from Narayanan, Manchanda & Chintagunta (2003)

Mizik & Jacobson (2004) studied data from a physician panel with 24 months of observations, in order to quantify the magnitude of the effects of two promotion instruments on the number of new prescriptions. They found that both detailing and drug sampling provoked positive effects, with detailing having the highest effect 1,56 for brand A, 0,32 for brand B, and 0,153 for brand C, whereas the coefficients for drug sampling were 0,155, 0,039 and 0,014 for brands A, B and C, respectively (table 5.12).

Table 5.12 - Promotion tools regression coefficients - Mizik & Jacobson (2004)

	Regression coefficients		
	Brand A	Brand B	Brand C
Detailing	1,56	0,32	0,153
Drug sampling	0,155	0,039	0,014

Source: Adapted from Mizik & Jacobson (2004)

Narayanan, Desiraju & Chintagunta (2004), when studying the interactions of promotion instruments using data from the anti-histamines market, also found that detailing has the stronger effect on sales. In their model, DTCA appears second, and an aggregation of meetings, seminars and medical journal advertising appears as third (table 5.13).

Table 5.13 - Promotion tools elasticities - Narayanan, Desiraju & Chintagunta (2004)

	Elasticities
Detailing	0,2853
Direct-to-consumer advertising	0,1946
Meetings and seminars + medical journal advertising	0,0521

Source: Adapted from Narayanan, Desiraju & Chintagunta (2004)

Narayanan, Manchanda & Chintagunta (2005) studied the changing role of marketing communication over the life cycle of a new product category, and analyzed three drugs in the antihistamines market. When assessing the comparative importance of promotion tools in terms of physicians' prescribing behavior, they found that detailing score first in terms of elasticities, followed by a category consisting of meetings, seminars and medical journal advertising, and by DTCA. The elasticities found in their research are shown below in table 5.14.

Table 5.14 – Promotion tools elasticities - Narayanan, Manchanda & Chintagunta (2005)

	Elasticities		
	Allegra	Claritin	Zyrtec
Detailing	0,0912	0,0867	0,0795
Meetings and seminars + medical journal advertising	0,0389	0,0191	0,0317
Direct-to-consumer advertising	0,0132	0,0162	0,0123

Source: Adapted from Narayanan, Manchanda & Chintagunta (2005)

Kalyanaram (2008) studied the effects of order of market entry on market share in prescription and over-the-counter market, using data on sales, direct-to-physician promotion (aggregating detailing and Medical Journal advertising), and DTCA. They found that direct-to-physician promotion has a much higher elasticity than DTCA, both for prescription and over-the-counter drugs. The elasticities are shown below in table 5.15.

Table 5.15 – Promotion tools elasticities - Kalyanaram (2008)

	Elasticities	
	Prescription drugs	Over-the-counter drugs
Detailing + medical journal advertising aggregation	0,81	0,69
Direct-to-consumer advertising	0,12	0,31

Source: Adapted from Kalyanaram (2008)

Vakratsas & Kolsarici (2008) studied a therapeutic class using class aggregated data, using detailing, DTCA and medical journal advertising. They found that detailing coefficients were not significant (probably due to saturation, or to the fact that the data was aggregated by class). Medical journal advertising and DTCA yielded positive elasticities (table 5.16).

Table 5.16 - Promotion tools elasticities - Vakratsas & Kolsarici (2008)

	Elasticities
Medical Journal advertising	0,07
DTCA	0,06
Detailing	N/S

Source: Adapted from Vakratsas & Kolsarici (2008)

Kalyanaram (2009), when analyzing promotion elasticities for three therapeutic classes of prescription drugs, concluded again that direct-to-physician promotion has a much higher elasticity than DTCA. The elasticities are shown below in table 5.17

Table 5.17 – Promotion tools elasticities - Kalyanaram (2009)

	Elasticities
Detailing + medical journal advertising aggregation	0,62
Direct-to-consumer advertising	0,21

Source: Adapted from Kalyanaram (2009)

There is however a limitation inherent to these two research articles (Kalyanara, 2008; Kalyanara, 2009), on the relative magnitude of importance of detailing and medical journal advertising. Because the two promotion instruments were grouped into one single tool called direct-to-physician promotion, it is not possible to isolate the detailing elasticity in both papers.

Leeflang & Wieringa (2010) studied the impact of detailing, medical journal advertising, and direct mail advertising on the number of prescriptions of 49 drug brands in the Netherlands. On the very limited number of brands which produced significant and positive elasticity coefficients (of the right signal), medical journal advertising had the highest elasticity, followed by detailing and direct mail advertising (all three promotion tools evidenced, as shown in table 5.18 below, very modest elasticities).

Table 5.18 - Promotion tools elasticities - Leeflang & Wieringa (2010)

	Elasticities
Medical Journal advertising	0,027
Detailing	0,014
Direct mail advertising	0,007

Source: adapted from Leeflang & Wieringa (2010)

Montoya, Netzer & Jedidi (2010), in their research of a dynamical allocation model of detailing and drug sampling, found that both promotion tools yielded positive elasticities, as seen in table 5.19.

Table 5.19 - Promotion tools elasticities - Montoya, Netzer & Jedidi (2010)

	Elasticities
Detailing	0,654
Drug sampling	0,253

Source: adapted from Montoya, Netzer & Jedidi (2010)

Very limited research has been conducted addressing the effectiveness of e-detailing in terms of drug sales. Gönül & Carter (2010) investigated the impact of both detailing and e-detailing on the number of new prescriptions for 21 prescription medicines, and found that both promotion tools had positive standardized coefficient in a multiple regression. Detailing had a stronger coefficient than e-detailing (0,509 vs 0,384). Interestingly, the coefficient of the interaction of both promotion tools appeared negative, as shown below in table 5.20.

Table 5.20 - Promotion tools regression standardized coefficients - Gönül & Carter (2010)

	Standardized coefficients
Detailing	0,509
e-Detailing	0,384
Detailing x e-Detailing interaction	-0,513

Source: Adapted from Gönül & Carter (2010)

Dave & Saffer (2012) studied the effect of DTCA on pharmaceutical prices and demand, controlling for physician-directed promotion. Analyzing four therapeutic classes using US-based data, they found that detailing is much more influential than drug sampling and DTCA in impacting sales. The elasticities found are shown below in table 5.21.

Table 5.21 - Promotion tools elasticities - Dave & Saffer (2012)

	Elasticities
Detailing	0,51
Drug sampling	0,34
Direct-to-consumer advertising	0,13 to 0,19

Source: Adapted from Dave & Saffer (2012)

More recently, Mukherji, Jaimakiraman, Dutta & Rajiv (2017) studied DTCA effect on prescriptions of four branded cholesterol-reducing drugs (statins), and found that detailing has a substantially higher effect than DTCA in individual drug choice (approximately 2,3 times more). These evidences are shown below in table 5.22.

Table 5.22 - Promotion tools parameters - Mukherji, Jaimakiraman, Dutta & Rajiv (2017)

	Parameters
Detailing	0,000112
Direct-to-consumer advertising	0,0000478

Source: Adapted from Mukherji, Jaimakiraman, Dutta & Rajiv (2017)

Based on the research addressed in the last pages regarding the effectiveness of several promotion instruments (by means of previous research using time-series), a summary table was developed, shown below (table 5.23).

Table 5.23 – Comparative analysis of promotion instruments effectiveness on impacting physician prescription behavior

	Comparative analysis of promotion instruments effectiveness on impacting physician prescription behavior (time-series based) (prescription vs promotion investments data)															
Theoretical grounding / Promotion instruments	Montgomery & Silk (1972)	Berndt, Bui, Reiley & Urban (1995)	Gönül et al (2001)	Narayanan, Manchanda & Chintagunta (2003)	Mizik & Jacobson (2004)	Narayanan, Desiraju & Chintagunta (2004)	Narayanan, Manchanda & Chintagunta (2005)	Kalyanaram (2008)	Kremer, Bijmolt, Leeflang & Wieringa (2008)	Vakratsas & Kolsarici (2008)	Kalyanaram (2009)	Gönül & Carter (2010)	Leeflang & Wieringa (2010)	Montoya, Netzer & Jedidi (2010)	Dave & Saffer (2012)	Mukherji, Jaimakiraman, Dutta & Rajiv (2017)
Detailing (sales calls)		1st	1st	1st	1st	1st	1st		1st			1st	2nd	1st	1st	1st
Detailing + medical journal advertising aggregation								1st			1st					
Medical Journal advertising	1st	2nd							2nd	1st			1st			
Drug sampling			2nd		2nd									2nd	2nd	
Meetings and seminars + medical journal advertising aggregation				2nd		3rd	2nd									
DTCA		3rd		3rd		2nd	3rd	2nd	3rd	2nd	2nd				3rd	2nd
e-Detailing												2nd				
Direct mail advertising	2nd												3rd			
Meetings + Direct mail advertising + drug sampling									4th							

Source: own elaboration

Some conclusions can be drawn from table 5.23. First, detailing – as seen before - appears to be the most influential promotion tool. By considering the predicted elasticities proposed by Kremer, Bijmolt, Leeflang & Wieringa (2008), detailing is 2,7 times as influential as medical journal advertising (second in terms of influence), 4,5 times as influential as DTCA (ranked third), and 5,3 times as influential as other direct-to-physician promotion tools. Using a similar approach, we computed the averages of the elasticities of the promotion instruments covered in the last pages (excluding research that did not present elasticities), and the results are shown in table 5.24 below (by memory, elasticity translates the percentage change in sales (or prescriptions), for every percentage change in the promotion tool investments, as explained by Narayanan, Desiraju & Chintagunta, 2004).

Table 5.24 – Calculated average elasticities of promotion instruments

	Average elasticity	Nr of cases
Detailing + medical journal advertising aggregation	0,71	3
Detailing (sales calls)	0,25	12
Drug sampling	0,16	5
Medical Journal advertising	0,15	5
DTCA	0,08	13
Meetings + Direct mail advertising + drug sampling	0,06	1
Meetings and seminars + medical journal advertising aggregation	0,04	7
Direct mail advertising	0,01	2

Source: own calculations based on previous tables

Table 5.24 evidences that detailing appears to be the most effective pharmaceutical promotion instrument, followed by drug sampling, medical journal advertising, and DTCA. This analysis incorporates a series of limitations that should be considered. First, the literature review conducted was not systematic, and therefore a substantial fraction of the literature on pharmaceutical marketing may not be reflected; second, the number of cases (articles) in each

promotion instrument is not the same (in some cases there is only one eliglble article), which demands the necessary prudence in interpreting the calculated averages; third, some of the promotion tools are aggregated, which does not allow a deeper individual level analysis; fourth, the selected papers do not address the impact of other promotion instruments such as gifts and meals, continuing medical education and event sponsoring (given that, to the best of our knowledge, previous research was not extant using time-series analysis), and more recent promotion tools using digital communication channels (such as e-detailing, e-sampling, or e-mailing); fifth, and related to the previous limitation, the average elasticity coefficients shown here may not constitute the precise real values of the elasticities. Should all the covered promotion instruments had been evaluated in the same research using time-series data, individual elasticity coefficients would therefore not only be more precise, but also allow for a better comparison of the relative magnitude of their effect on prescription behavior. This situation allows definite room for future research on pharmaceutical promotion tools.

However, and despite the listed limitations, the analysis evidenced in table 5.24 tries to fill a limitation present in Kremer, Bijmolt, Leeflang & Wieringa (2008) research, which is the aggregation of drug sampling (a very important promotion instrument with a substantial effect on the number of prescriptions) as an independent promotion instrument (their research merged it in a category named "Other direct-to-physician promotion tools"). Another point is that, more than analizing the precision of the individual elasticity coefficients, table 5.24 is intended at helping understand the relative magnitude of the impact of several promotion instruments.

5.8.6. Ethical considerations

Several authors have suggested that physicians may not be immune to pharmaceutical industry influence on prescription drugs choice. The possibility that this influence may negatively impact therapeutic decisions or involve additional costs to patients and health systems has been studied by some researchers.

Wazana (2000) noted in his review that most studies addressed some negative outcomes associated with the interaction between the pharmaceutical industry and physicians. These included a series of effects, including a negative impact on physicians' ability to identify wrong claims about medication; effects on «*awareness, preference, and rapid prescription of a new drug*» (p. 378); effects on physicians' behavior, by «*making formulary requests for*

medications that rarely held important advantages over existing ones» (p. 387); also included «*nonrational prescribing behavior; increasing prescription rate; prescribing fewer generic but more expensive, newer medications at no demonstrated advantage*» (p. 378). Datta & Dave (2016) hypothesized that, if the detailed drugs cost more than other alternatives, then the detailed-induced increase in prescriptions may contribute to higher overall prescription drug spending, at the expense of the patient (directly or indirectly) and of the health systems.

Bekelman, Li & Gross (2003) studied, in their review of the scope and impact of financial conflicts of interest in biomedical research, highlighted that «*approximately one fourth of investigators have industry affiliations, and roughly two thirds of academic institutions hold equity in start-ups that sponsor research performed by the same institutions*» (p. 454). The researchers found an association between industry sponsorship and pro-industry conclusion, with an odds ratio of 3,60.

Qualitative research developed by Skandrani & Sghaier (2016) highlighted some unethical behaviors of pharmaceutical sales representatives, such as providing misleading and incomplete information to physicians, giving incentives, discrediting competitors and misusing samples.

A study developed by Johansen & Richardson (2016) suggested that an estimation of $73 billion could have been avoided in excess of generic cost, when a generic alternative is available to substitute brand drugs, in the US in the period between 2010 and 2012. They also suggested that two thirds of this amount were born by the payers, and one third by the patients as out-of-pocket expenses. Given that restrictions on promotion activities developed by the pharmaceutical industry directed to prescribers have been demonstrated to increase the use of generic drugs (Larkin et al, 2017), and that promotion activities directed to patients (DTCA) can influence physicians' prescription behavior toward the brand requested by the patient (Kravitz et al, 2005), a holistic discussion between the main stakeholders of the industry – from manufacturers to policy makers - may be opportune.

Off-label promotion through detailing, that is, promoting of a drug for a different use that has not been authorized by the Food and Drug Administration (FDA) is illegal, as underlined by Shapiro (2018). He noted that, since 2004, more than 30 federal cases were settled involving off-label promotion activities by pharmaceutical manufacturers, in excess of $12 billion. Shapiro (2018) studied the extent to which detailing may cause undesirable prescriptions in the scope of the antipsychotics crug class, and found that the impact of detailing on off-label

physician prescriptions is modest, both in absolute and in relative terms. For instance, the marginal effect of one extra visit increases off-label prescriptions by only 0,038 in the present month. Radley, Finkelstein & Stafford (2006) studied phsycians prescribing patterns for 160 commonly prescribed drugs, and found that off-label prescription is common in outpatient settings, and that in almost three out of four cases, there was either no scientific support or little scientific backup for the prescription choice.

5.8.7. Sub-chapter synthesis of main findings

This subchapter covered several perspectives concerning pharmaceutical promotion tools. It started with stakeholders' perspectives about pharmaceutical manufacturers' promotion of prescription drugs to physicians. Pharmaceutical manufacturers, through PhRMA, defend their legitimacy to promote prescription drugs based on the facts that they provide physicians with FDA-regulated education and scientific information. They also allege that pharmaceutical marketing is only one of the factors physicians consider in the prescription choice. They also state that a vast majority of physicians find information provided by PSRs as useful and reliable, and that marketing activities may allow more patients to have earlier access to innovative treatment options. Physicians' perceptions about the interactions developed with PSRs evidence mixed results. Some literature highlights positive perceptions, consisting of the recognized importance as a source of information, and also convenience and accessibility, since the method typically uses a face to face contact. Physicians tend to consider educational gifts as appropriate, whereas recreational gifts are considered less appropriate. Physicians also tend to value the drug samples PSRs offer them, whose benefit is passed to the patient, and the knowledge gathered during meetings with PSRs. However, there are negative perceptions too. PSRs may constrain doctors' agendas, present commercially-biased information, and incorrect influence on prescribing. Interestingly, doctors do not perceive themselves as influenced by pharmaceutical marketing as their peers, revealing an apparent perception of immunity against pharmaceutical marketing initiatives.

Pharmaceutical sales representatives consider their work as crucial, believing that they have a considerable influence on physicians' prescription choices. PSRs consider the communication skills as the most important attribute in drug promotion. Non-prescribing clinicians' perspectives were also approached. Nurses have also been targeted by pharmaceutical manufacturers through detailing, training, drug samples, gifts and meals. They may recommend treatments to physicians and provide patients with advice about non-prescription medicines, and therefore influence prescriptions.

Pharmacists have also been targeted by pharmaceutical industry marketing, and generally have a positive perception of it. They too are visited by PSRs, receive education and other services, and can influence physicians prescription choices, based on what they know about the patients. Patients seem to reveal a high awareness of some of the promotion tools pharmaceutical manufacturers employ in their interactions with physicians. They reveal higher awareness about and acceptance of drug samples, and office gifts such as ball pens, but reveal a lower awareness and also lower acceptance of personal gifts and meals, considering more expensive gifts as less appropriate. These results confirm that physicians are not the only professionals being target by pharmaceutical industry marketing, and that other stakeholders are aware of the interactions between physicians and pharmaceutical manufacturers.

The sub-chapter then explicated that the pharmaceutical industry is one of the industries where pharmaceutical manufacturers use a combination of both push and pull promotion, combining detailing and tools using digital channels to both push messages and encouraging physicians to have the initiative of retrieving and asking for additional contents. The literature on physicians' preferences on digital channels is scant, and therefore some non-peer reviewed sources were consulted. Evidence from the practice suggests that different physician specialties react differently to promotion using digital channels, in terms of preference. The same evidence appears to be seen when considering different countries, where for instance doctors from European countries appear to evidence a higher willingness to be targeted by digital channels, when comparing results against Japan and the USA. Promotion using digital channels appears to evidence relevant affinity levels, with doctors appearing to reveal favorable attitudes, but varying substantially among medical specialties. A different concept is physicians' prescription attitude on digital channels, which appears to evidence, according to research conducted by consulting firms, lower prescription intention when compared to promotion using traditional channels (again, with differences among countries).

The sub-chapter ended with the discussion of ethical issues in the scope of pharmaceutical industry promotion of prescription drugs to physicians. The conclusion is that physicians are not immune to this promotion, which may negatively impact their prescription behavior. These negative outcomes include a negative impact on physicians' ability to identify wrong claims about medication, effects on awareness, preference, and prescription of a new drug, effects on physicians' behavior, nonrational prescribing behavior, increasing prescription rate, and prescription of fewer generic but more expensive medications at no evidenced benefit.

This may contribute to higher overall prescription drug spending, at the expense of both the patients and the payers. Unethical practices from the industry include providing misleading and incomplete information to physicians, giving incentives, discrediting competitors and misusing drug samples.

5.9.Chapter synthesis of main findings

The present chapter addressed literature on pharmaceutical industry promotion. It underlined the importance of marketing communication, process by which pharmaceutical manufacturers convey messages to several stakeholders including physicians. It also explained the difference between communication channels – means, or vehicles through which the message moves from the sender to the receiver – and promotion tools - instruments used by companies to develop interaction with clients and reach promotion goals, using communication channels. Communication channels – face-to-face, telephone, mail, print, television and on-line – can be classified as personal versus nonpersonal, and traditional versus digital. Promotion tools include a series of instruments used by pharmaceutical manufacturers to interact with physicians, including detailing, drug sampling, gifts and meals, continuing medical education (CME) and event sponsoring (conventions, meetings, conferences, seminars, lectures, symposia), direct-mail advertising, medical journal advertising, direct-to-consumer advertising (DTCA), e-detailing, e-mail marketing, e-Continuing medical education (e-CME), company websites and healthcare portals, health social networks, e-sampling, and e-Direct-to-consumer advertising (e-DTCA) in the scope of Web 2.0. These promotion tools can be positioned in a communication channels foundation (here illustrated in figure 5.22, in a continuum from traditional to digital, and from nonpersonal to personal).

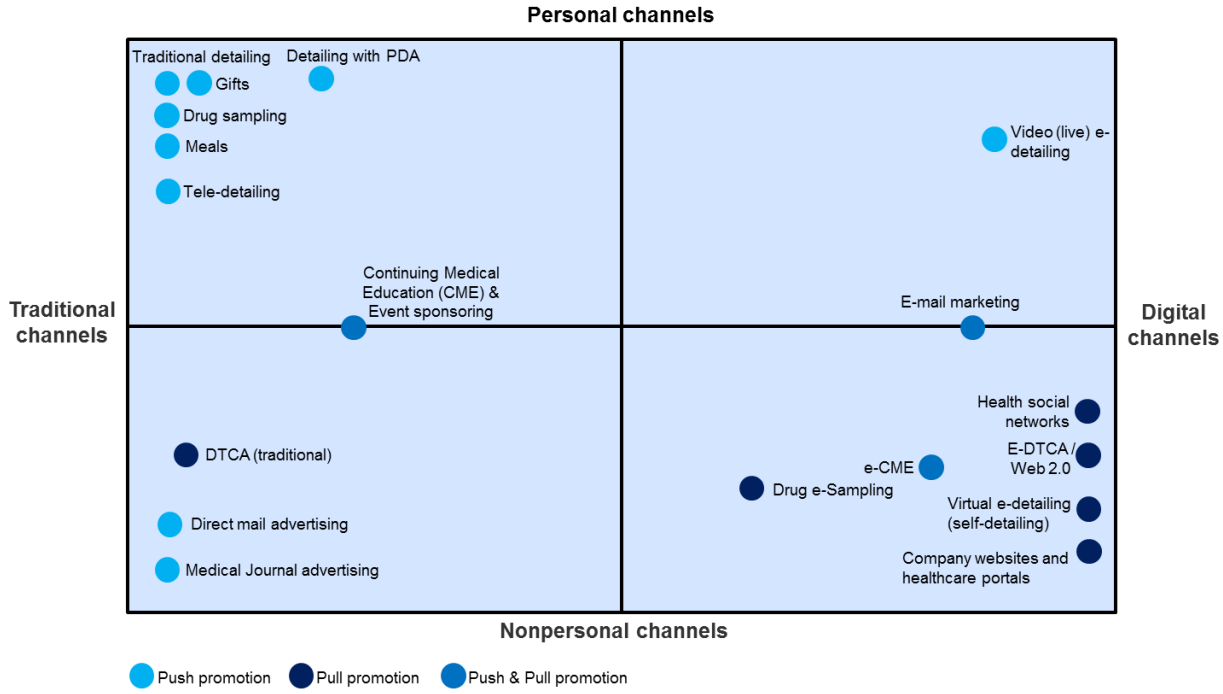


Figure 5.22 - Pharmaceutical companies' spectrum of promotion instruments

Source: adapted from Bernewitz (2001)

The most important promotion instrument, both in terms of investment magnitude, and in terms of impact on prescription behavior, is detailing, a form of personal selling and a form of relational marketing, where a pharmaceutical sales representative visits individual doctors, and provides information about his or her company's drugs. A series of theoretical evidences were shown, here listed: the effect of detailing on brand prescriptions is significant and on average positive, but small; detailing appears to be the promotion instrument that generates a higher effect on prescription behavior; detailing appears to reduce price elasticity of drugs (reduces physicians' price sensitivity); detailing effect on prescription behavior seems to evidence diminishing marginal returns; detailing efforts appear to have a higher effect on prescriptions at the initial stages of the product life cycle; detailing seems to evidence carry-over effects; detailing effect on prescriptions appears to be more on drug shares, rather than on drug category volume; detailing may have different effects on prescription, depending on the type of payer (physicians mostly seeing patients with private health insurance seem to be more prone to be influenced by detailing); detailing elasticities depend on the therapeutic or disease classes; detailing may be linked with physician nonrational prescription behavior; detailing effect may be leveraged by selecting the right key opinion leaders to impact (social

multiplier); gifts and meals associated with detailing may impact prescription behavior; recipients of the detailing activities (prescribers) do not consider themselves as influenced as their colleagues; detailing effectiveness can be optimized, in order to reach higher levels of sales force efficiency; certain physician profiles and situations increment the likelihood of a more frequent interaction between physicians and PSRs; detailing effectiveness can be attenuated by a form of detailing called academic detailing.

Detailing faces several challenges as a pharmaceutical promotion tool. It is quite expensive, access to physicians is increasingly difficult, health care institutions are putting pressure on doctors in terms of payment (resulting in more patients to attend), and restrictions on PSRs' access to physicians have been implemented in some countries.

Other promotion instruments using traditional communication channels were addressed. Drug sampling has been demonstrated to impact physicians' prescription behavior in favor of the offered drug samples. Gifts and meals have also been shown to influence physician prescription behavior. Medical journal advertising is one of the least expensive promotion tools, and direct mail advertising can reach a substantial number of physicians, complementing detailing activities. Continuing medical education has been used by pharmaceutical manufacturers to help physicians keep up-to-date in their practices, including funding for travel or lodging for educational symposia and meals). Direct-to-consumer advertising has been demonstrated to impact both patients' and physicians' behavior regarding prescription drug choices.

This chapter also covered promotion tools using digital communication channels, which still represent a very small percentage of the total promotion investments. These tools include e-detailing, e-sampling, company websites and healthcare portals, health social networks, e-mailing, online continuing medical education (e-CME), and e-Direct-to-consumer advertising, in the scope of Web 2.0. E-detailing – the most utilized promotion tool using digital channels – brings several benefits to physicians and to pharmaceutical manufacturers, and has been shown to positively impact prescriptions of the promoted drugs, when used in combination with traditional detailing. Other promotion tools using digital channels were addressed. E-sampling allows physicians to request drug samples through a website or a health care portal, company websites and health care portals can be used to connect several stakeholders, health social networks can offer manufacturers the ability to post high impact banner ads targeted to specific physicians, e-mail marketing allows manufacturers to send targeted content to specific physician audiences, online continuing medical education can be used by

pharmaceutical manufacturers to interact with physicians in the scope of training and education. Pharmaceutical manufacturers can also use e-direct-to-consumer advertising to impact the general population, in the scope of Web 2.0.

Several perspectives concerning pharmaceutical promotion tools of prescription drugs, directed at physicians, were also addressed. Pharmaceutical manufacturers defend their legitimacy to promote prescription drugs based on the facts that they provide physicians with FDA-regulated education and scientific information, that information provided by PSRs is useful and reliable, and that marketing activities may allow more patients to have earlier access to innovative treatment options. Physicians have both positive and negative perceptions about the interactions with PSRs. While these interactions can be a source of information, convenience and accessibility to doctors, PSRs may constrain doctors' agendas, present commercially-biased information, and incorrect influence on prescribing. Nevertheless, research has demonstrated that physicians tend to consider themselves immune against pharmaceutical marketing initiatives. PSRs consider their work as crucial, believing that they have a considerable influence on physicians' prescription choices. Non-prescribing clinicians' perspectives were also approached.

Nurses have also been targeted by pharmaceutical manufacturers through detailing, training, drug samples, gifts and meals. Pharmacists have also been targeted by pharmaceutical industry marketing, through detailing, education and other services. Patients seem to reveal high awareness and acceptance of some of the promotion tools pharmaceutical manufacturers employ in their interactions with physicians (office-based gifts), but reveal a lower awareness and acceptance of personal gifts and meals, considering more expensive gifts as less appropriate.

The chapter then addressed the push and pull character of prescription drugs pharmaceutical promotion, highlighting that this industry is one of the ones using a combination of both push and pull promotion, combining detailing and tools using digital channels to both push messages and encouraging physicians to have the initiative of retrieving and asking for additional contents. Different physician specialties react differently to promotion using digital channels, in terms of preference, and the same when considering physicians from different countries. In terms of its declared impact on prescription behavior, promotion using digital channels appears to evidence lower prescription intention, when compared to promotion using traditional channels. The chapter also addressed ethical issues related to prescription drug promotion by pharmaceutical manufacturers. Some negative outcomes can appear, such as

doctors reduced ability to identify wrong claims, nonrational prescribing behavior, increased prescription rate of expensive drugs at the expense of generics, and provision of misleading and incomplete information.

6. Regulation of pharmaceutical marketing activities

6.1.Content and logic of the chapter

This chapter addresses the theories on regulation of pharmaceutical marketing activities on prescription drugs, directed at physicians. A first sub-chapter will address the main concepts related to this research area. Then, it will approach self-regulation, highlighting the several initiatives pharmaceutical manufacturers, pharmaceutical manufacturers associations, physician chambers and healthcare organizations have taken to self-regulate promotional activities in their interactions with physicians. Following, the chapter will address government regulation initiatives, aimed at regulating drugs price, physician prescription budgets, patient payment policies, direct-to-consumer advertising, and marketing efforts to physicians. The chapter also includes an analysis of the effectiveness of the several regulation initiatives, ending with the synthesis of the main findings gathered during the chapter.

6.2.Concepts

Several types of initiatives have been developed in the last decades, with the goal of regulating the pharmaceutical marketing activities deployed by pharmaceutical manufacturers in their interactions with health care providers, especially physicians. These initiatives can be self-imposed in the sense that they are voluntarily developed and implemented (in the case of pharmaceutical manufacturers, pharmaceutical manufacturers' national and international associations, physician chambers, and healthcare institutions), or legally compulsory (if imposed by the government through the health tutelage).

A series of reasons may explain these initiatives to regulate pharmaceutical marketing. Patients are becoming more demanding in terms of transparency and empowered regarding information about the industry. Shaw & Whitney (2016) noted that «*as consumers become more enlightened and empowered to learn about the industry, many companies have developed their strategies to ensure a transparent relationship between industry and consumer*» (p. 201). Patients and the general public are also more alert to physician interactions with the industry. Fadlallah et al (2016) acknowledged, in their review, that patients and the general public supported the disclosure of these interactions through easy-to-read printed documents and verbally during the consultations. These reasons, allied to growing literature demonstrating the effects of promotion activities on prescription behavior, and of health expenditures rising pressure on public budgets, contributed to the need to increase the regulation, transparency and disclosure in the relations between physicians and manufacturers.

6.3.Self-regulation

In this topic, we will address self-regulation developed by pharmaceutical manufacturers, pharmaceutical manufacturer national and international associations, physician chambers and health care organizations, to regulate the interactions between manufacturers and physicians.

6.3.1. Pharmaceutical manufacturers

Pharmaceutical manufacturers have been proactively developing initiatives (mainly self-regulatory codes of conduct) to auto-regulate their activities with HCPs and HCOs. At individual company level, many companies have been creating their own codes of conduct, such as Johnson & Johnson (2016), Pfizer (2016), Merck (2016), Novartis (2016), Roche (2016), Sanofi Aventis (2016) and AstraZeneca (2016), to list a few of the top pharmaceutical and biotech companies in terms of revenues (Forbes, 2015). These regulations may not however be impactful in terms of effect production. Roughead, Gilbert & Harvey (1998) studied tape recorded interactions between GPs and PSRs, concluding that PSRs presentations to physicians may not always comply with standards defined by companies' codes of conduct. They suggested that policy regulation of PSRs activities is necessary to contribute to the adequate use of medicines. Norris, Herxheimer, Lexchin & Mansfield (2005) reviewed studies on drug promotion and concluded that the guidelines and regulations that should control PSRs activities are not effective. Francer et al (2014) called these initiatives company standards, where manufacturers develop and implement codes of conduct and internal compliance and audit organizations to impose them.

6.3.2. Pharmaceutical manufacturers associations

According to Lexchin (1997), some or the totality of the promotional activities of pharmaceutical companies are generally governed by self-regulatory codes administered by industry associations. He explained that «*industry self-regulatory codes lay down principles and practices to be observed in promotion in an attempt to balance commercial objectives with the ethical and scientific objectives of providing accurate information to prescribers*» (p. 352).

At national level, associations representing the manufacturers have been developing Codes of practice governing pharmaceutical companies. Francer et al (2014) called this independent local industry codes of practice. For instance, Pharmaceutical Research and Manufacturers of America (PhRMA) with its Code on Interactions with Healthcare Professionals (in the US), Association of the British Pharmaceutical Industry (ABPI) and its Code of Practice for the Pharmaceutical Industry (in the UK), Medicines Australia with it Medicines Australia Code

of Conduct, and Interfarma with its Brazilian Code of Conduct. In Canada, the Pharmaceutical Advertising Advisory Board (PAAB) has to give clearance to journal advertising, and to other promotion activities such as advertising and promotional messages carried via audio, visual, audiovisual, electronic and computer means of communication with physicians. From the pharmaceutical manufacturers' side, there is the Code of Marketing practices of the Pharmaceutical Manufacturers Association of Canada (PMAC). Lexchin (1997) explained that PMAC member must agree to accept the PAAB code, and also the journal insert guidelines from the Association of Medical Media. In Portugal, APIFARMA is the association representing the pharmaceutical manufacturers. APIFARMA has been developing and updating its code of ethics since 1987, adapting it to national and European Union legislation. This code of ethics is called "Código deontológico para as práticas promocionais da indústria farmacêutica e para as interacções com os profissionais de saúde e instituições, organizações ou associações constituídas por profissionais de saúde".

As highlighted by Francer et al (2014), at global level, International Federation of Pharmaceutical Manufacturers and Associations has developed its IFPMA Code of Practice, and at regional level there are two main associations, one at Central America scope (Federación Centroamericana de Laboratorios Farmacéuticos (FEDEFARMA), with its Code of Good Practices for the Promotion of Medicines), and one at European scope (European Federation of Pharmaceutical Industries and Associations (EPFIA)). EFPIA, an institution representing the national industry associations from European countries, developed a transparency code called EFPIA code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals (HCPs) and healthcare organizations (HCOs).

Pharmaceutical manufacturers associations not only are developing initiatives to regulation their interactions with HCPs and HCOs, but also to manage the disclosure of their activities to the general public. In order to comply with EFPIA, members were asked to transpose the code to their national codes, at the same time observing national laws and regulations on disclosure. APIFARMA adapted its code of ethics to incorporate EFPIA's best transparency practices, resulting in APIFARMA current code of ethics for promotion practices of the pharmaceutical industry and interaction with health care professionals and institutions, organizations or associations comprising health care professionals (EFPIA, 2016b). In Portugal, APIFARMA members are now obliged to observe not only the national legislation on transfers of value disclosure, but also APIFARMA's code of conduct, which requires members to disclose eligible transfers of value made to HCPs and to HCOs on a yearly basis.

This disclosure is made at PLACOTRANS (2017), an INFARMED on-line platform dedicated to transparency.

Figure 6.1 below, proposed by Francer et al (2014), highlights the different codes and regulatory mechanisms applying to international pharmaceutical companies.

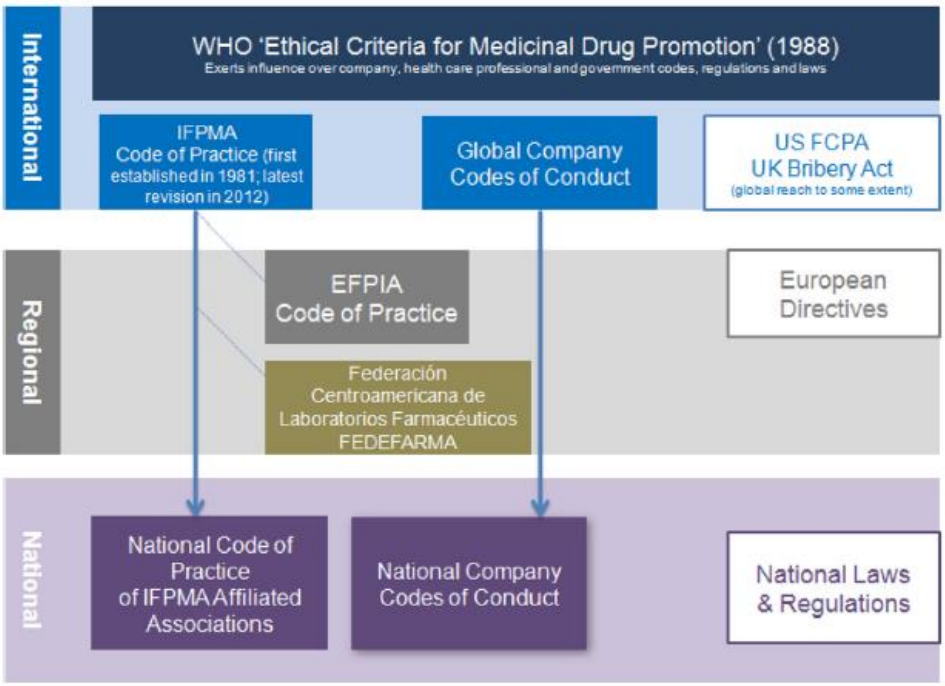


Figure 6.1 - Different codes and regulatory mechanisms applying to international pharmaceutical companies

Source: Francer et al (2014)

6.3.3. Physician chambers

Francer et al (2014) addressed another system for controlling prescription medicines advertising, called professional bodies' codes of practice. Professional HCPs chambers also have developed codes of conduct to guide the interactions of their members with pharmaceutical manufacturers. For instance, the Portuguese Physician Chamber (Ordem dos Médicos) deontological code sets not only the standard for proper medical care given by patients, but also the principles for the physicians relations with the pharmaceutical industry (Ordem dos Médicos, 2016). The US, British and French equivalents are the American Medical Association Code of Medical Ethics (AMA, 2016), the British Medical Association (BMA) Ethics (BMA, 2016), and the French Ordre National des Medicins (ONM) Code of Medical Ethics (ONM, 2016).

Chambers guidelines may be developed to raise professional standards and transparency, with the goal of keeping high levels of credibility in the medical profession. How do the general public view healthcare practitioners ethical standards? Gallup, a US private company delivering analytics, has been developing Gallup Poll Social Series since 2001, monitoring U.S. adults' views on social, economic, and political topics. One of the surveyed topics is related to the surveyed participants' perceptions about the honesty and ethical standards of a selection of professions. Nurses scored first and have been reaching at least 80% of "Very high" plus "High" classifications since 2005. In 2016 wave, Pharmacists and Medical doctors ranked second and third, respectively (Gallup, 2017).

6.3.4. Healthcare organizations

Healthcare organizations have also been developing guidelines to regulate their collaborators (physicians and other healthcare professionals) interactions with pharmaceutical manufacturers. These guidelines vary substantially between institutions though, as noted by Norris, Herxheimer, Lexchin & Mansfield (2005), in their review, when analyzing guidelines to regulate interactions between pharmaceutical manufacturers (through PSRs) and medical trainees.

Austad, Avorn, Franklin & Kesselheim (2011) found, in their review, that medical students have substantial contact with pharmaceutical companies marketing, and that marketing is associated with positive attitudes and skepticism about negative implications of this contact. Some authors suggest that medical students' education on how to deal with pharmaceutical industry marketing might result in higher awareness about potential medical inducements. This was demonstrated by Vinson, McCandless & Hosokawa (1993) where a one-hour lecture and discussion about the appropriateness of pharmaceutical gifts resulted in higher awareness of students and higher resistance to accept gifts from the pharmaceutical industry. Wilkes & Hoffman (2001) demonstrated that medical student's attitudes in relation to pharmaceutical industry marketing changed after students received an educational program on the effect of pharmaceutical manufacturers on physicians' behavior. Significant results were found between a first survey and a second survey on ethical considerations regarding some pharmaceutical industry marketing tools.

Siddiqui et al (2014) highlighted the imperativeness that every medical college may «*incorporate guidance regarding doctor pharmaceutical interactions, practice clear ethical policies which medical students should be aware of, and help foster a supportive environment regarding such social issues so that our future physicians are more apt to handle them after*

demonstrating a high level of medical students' acceptability towards incentives and gifts given by the pharmaceutical industry» (p. 9), given that medical students revealed a high level of acceptability in relation to incentives given by pharmaceutical industry.

Sarikaya et al (2009) had also demonstrated that deliberate targeting of students by pharmaceutical companies' representatives was correlated with being less sensitive to the negative effects of, and having favorable opinions about interactions with pharmaceutical companies. Lieb & Koch (2013) also evidenced that students have a widespread contact with the pharmaceutical industry even during their first years as medical students. Similarly, the authors address the need to include specific curriculum regarding the pharmaceutical industry influence on prescription behavior, helping students to be aware of this influence and be have a more critical attitude. Steinman et al (2001) suggested that there is lack of formal education on pharmaceutical industry relations with residents, also underlining that doctors in training may be influenced by observing their mentors and colleagues receiving gifts from the industry, giving it an "implicit seal of approval".

Research has therefore demonstrated the importance of formal education on interactions between residents and pharmaceutical manufacturers. As noted by Sergeant, Hodgetts, Godwin, Walker & McHenry (1996), institutions that have guidelines to regulate the interactions between the pharmaceutical industry and residents, and that hold a formal session for residents on their policy, generate a higher awareness of these guidelines, in comparison with residents from institutions where a formal session is not available. This underlines the importance of teaching residents on these guidelines. Sergeant et al (1996) concluded that «*formal discussion of the issues and role-modelling by faculty members may increase residents' compliance*» (p. 1247). This aspect was later addressed by Norris, Herxheimer, Lexchin & Mansfield (2005). In their review on pharmaceutical drug promotion, underlined that education on pharmaceutical industry promotion, even of short duration (from 40 minutes to three-hour modules, sometimes with discussion and role playing) may change health professionals attitudes and improve skills on dealing with PSRs claims, allowing a more structured approach.

6.4.Government regulation

Government regulation is compulsory in nature, with legally required observation by pharmaceutical industry stakeholders. Pharmaceutical industry regulation is substantially diverse across the globe, as highlighted by Stremersch & Lemmens (2009). In one extreme

they positioned the USA, as a non-regulated pharmaceutical market, and in the other extreme they positioned Belgium and France, fully regulated pharmaceutical markets (figure 6.2).

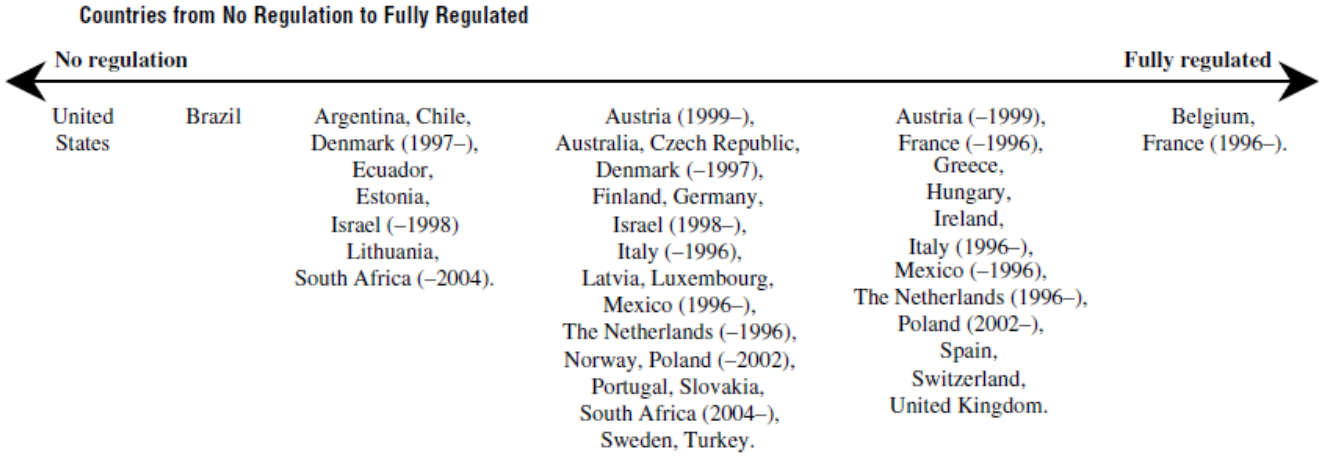


Figure 6.2 - Pharmaceutical Regulation by selected countries

Source: Stremersch & Lemmens (2009)

The pharmaceutical industry may be regulated in more than one dimension, as described in the following topics, following Stremersch & Lemmens (2009) framework.

6.4.1. Manufacturer price regulation

Price regulation is exerted by governments to control the manufacturers' price of drugs, imposing price restrictions irrespective of drug research and development and production costs, strategy applied in countries like Portugal, Greece, Belgium, Luxembourg, Ireland, The Netherlands, Switzerland, Norway and Finland, as highlighted by Stremersch & Lemmens (2009). These restrictions are higher in the European Union than in the US, where there is no price regulation (Golec & Vernon, 2010).

The impact of price regulation on the launch delay of new drugs was studied by Danzon, Wang & Wang (2005). Comparing data from 25 countries, including 14 European Union countries, they found that in countries with lower expected prices, or smaller expected market size, have less new drug launches and lengthier launch delays. They suggest a «*low price in one market may 'spill-over' to other markets, through parallel trade and external referencing, (and) manufacturers may rationally prefer longer delay or non-launch to accepting a relatively low price*» (p. 2). Danzon, Wang and Wang (2005) suggest their findings tend to validate the hypothesis that price regulation affects the timing and occurrence of drugs launch in a negative way. They suggest that countries that have stricter regulation on manufacturer

pricing also have habitually been key parallel exporters, where Portugal is included (as well as Italy, France, Belgium, Spain, and Greece).

Kyle (2007) has also studied the effect of pharmaceutical prices and entry strategies. She found that the use of price restrictions has a statistically and quantitatively substantial effect on the extent and timing of new drug launches: not only a delay or reduced probability in countries that impose the restrictions, but also into other markets as well, due to carry over effects, since these effects are not isolated in a single market, influencing global drug launch decisions. Kyle (2007) also suggests that drug launches in low price countries may suffer from additional delay after the legalization of parallel imports (approved in the EU in 1995), by which medicines wholesalers can purchase drugs in other EU countries, and develop price arbitrage (for instance buying in low-price countries and selling in high-price countries).

Manufacturer price regulation can have an impact on research and development spending, as evidenced by Golec & Vernon (2010), when analyzing the relationship between price regulation and R&D spending in EU and US firms. They found that EU price pharmaceutical restrictions have led to lower «profitability, stock returns and R&D spending by EU than with US firms. And this may have led to 46 fewer new medicines and 1680 fewer research jobs, in the EU.

Drug sales on countries with manufacturer price controls tend however to be higher than in countries without price controls (Stremersch & Lemmens, 2009). They suggest that price controls do not appear to constrain medicines availability to patients after a drug is launched.

6.4.2. Regulation on physician prescription budgets

Another type of regulation is physician prescription budgets, which have been set to contain pharmaceutical spending (Fischer, Koch, Kostev & Stargardt, 2017). This is the most direct way in which regulators can intercede in pharmaceutical markets for prescription drugs, through limitations on the total number of prescriptions issued by a physician, as suggested by Stremersch & Lemmens (2009). They referred the cases of Germany, where a collective budget for prescription drugs was implemented in the 1990s, and later reformed to physician-level prescription budgets, and Latvia, where a fixed budget by physician is calculated considering the number of patients in their practice.

Granlund, Rudholmand & Wikstrom (2006) studied the impact of a prescription fixed budget on two health centers in Sweden who have implemented a strict responsibility over the prescription budgets. They found that the introduction of pharmaceutical budgets did not

impact physicians' prescription behavior, neither in volume (quantity of drugs prescribed) nor in the cost of the prescriptions.

Conversely, other authors have demonstrated evidence of the impact of prescription budget regulation on the cost of prescriptions. Stremersch & Lemmens (2009) evidenced that regulation on physician prescription budgets had a significant negative impact on drug sales, but apparently more effective for mature drugs, while for more recently launched drugs the impact was smaller of inexistent. They also suggested that in regulated markets prescribers will feel more pressure to prescribe less expensive drugs to patients with milder symptoms or who can tolerate traditional alternatives well, prescribing more expensive drugs to patients with more severe symptoms. Fischer et al (2017) studied the cost and quality of prescribing, considering the level of utilization of drug budget using a panel of several hundred physicians in Germany, with data from 2005 to 2010. They found that physicians appear to be sensitive to the utilization of their drug budget in the previous year, by selecting brands more carefully and by increasing the generic share on prescriptions (but the total number of prescriptions did not suffer significant variations). They advocate that the German prescription budget (with sanctioning mechanics) did not change the number of prescriptions per medical consultation, but the average cost of the prescription was lower.

A government initiative that may appear in the scope (directly or indirectly) of physician prescription budgets is the mandatory generic substitution. It happens when, with the goal of reducing costs for off-patent medicines and increase the prescription of cheaper medicines (generics), physicians are obliged to prescribe a generic version of a drug (whenever applicable) which may have a significant impact on physician prescription behavior, as noted by Andersson, Petzold, Allebeck & Carlsten (2008). They studied the impact of the implementation of a mandatory generic substitution program in Sweden, and found that sales of substitutable pharmaceuticals evidenced proportionally larger growth when compared against sales of non-substitutable pharmaceuticals (that is, drugs that do not have yet generics competing against), suggesting that the impact of the substitution program was significant and positive in terms of sales growth of less expensive prescription options. Another effect was the reduction of prices of many substitutable products, due to increased competition.

6.4.3. Patient payment policies

According to Reuveni et al (2002), co-payment is a policy in which patients cover part of the cost of the medication. Luiza et al (2015) addressed, in their review, four types of payment policies, which can be set depending on the drugs included, the eligible patient groups, the

amount of money patients are expected to pay and the ways in which they are expected to pay. These can be a cap policy, where patients are reimbursed for the prescribed medicines up to a maximum amount in a certain period of time (and therefore pay the market price of medicines thereafter); can be a fixed co-payment policy, where patients pay a fixed amount per medicine or prescription, independently of the brands prescribed (it is also know by prescription charge, consumer charge, prescription fee, patient fee or cost sharing); can be a co-insurance policy, where patients pay a defined percentage of the price of the prescription or medicine, instead of a fixed fee (policy also known by co-payment or cost sharing); and can also be a ceiling policy, in which patients pay the full cost or part of the cost up to a certain threshold, above which patients are given medicines for free or at smaller cost.

The rationale behind the introduction of patient payment policies is to reduce medicines misuse, overuse and underuse, leading to a reduction in wasted resources and health hazards (Luiza et al, 2015).

Stremersch & Lemmens (2009) had already highlighted that patients may be requested to pay some form of co-payment for prescription drugs, system applied in countries like Portugal, Italy, and Hungary. For instance, in Portugal – a country using co-insurance payment -, the beneficiaries of the National Health System are eligible for drug price reimbursement, which can vary depending on the pathology and group of patients. Decree-Law no. 48-A / 2010, of May the 13th, amended by Decree-Law no. 106-A / 2010 of October the 1st, defines the possibility of reimbursement of medicines through a general and through a special scheme (dispensing of drugs both in pharmacies and in hospital pharmacies). The State's contribution to the price of the medicinal products for sale to the public is set according to four levels: A, with a reimbursement of 90%, B, with 69%, C, with 37%, and D, with 15%. In pharmacies, patients pay the differential price not covered by the reimbursement, and the pharmacy is later reimbursed by the State budget. The reimbursement levels vary according to the therapeutic indications of the drug, its use, the entities that prescribe it and even the increased consumption for patients suffering from certain pathologies (Ordinance no. 924-A / 2010, of September the 17th, amended by Administrative Rule no. 994-A / 2010, of September the 29th and by Ordinance no. 1056-B / 2010, of October the 14th) in the case they are not included in the list of medicines considered crucial for sustaining life (whose price is 100% reimbursed).

In terms of impact of patient payment policies, Reuveni et al (2002) suggested that co-payment for prescription drugs may lead to decreased drug use. Italy may be an example of what happens when a co-payment policy already in place is cancelled. At the end of 2000 the

co-payment policy was abolished, and in the first months of 2001 there was a very significant growth (30%) in pharmaceutical spending, as addressed by Stremersch & Lemmens, 2009. They found that patient co-payment regulation seems to result in a negative and constant effect, suggesting that in co-payment policies patients may be monetarily penalized for medicines usage. Luiza et al (2015), in their review of patient payment policies, proposed that «*cap and co-payment policies may reduce the use of medicines and reduce medicine expenditures for health insurers*» (p. 2). They also stressed that these policies «*may also reduce the use of life-sustaining medicines or medicines that are important in treating chronic, including symptomatic, conditions and, consequently, could increase the use of healthcare services*» (p. 2).

6.4.4. Regulation of direct-to-consumer advertising

Direct-to-consumer advertising (or DTCA) of prescription drugs, only permitted in New Zealand and the USA, and forbidden in all other countries, is another tool pharmaceutical marketers can use to influence patients (Stremersch & Lemmens, 2009).

A study conducted by Cegedim Strategic Data revealed that the top 20 pharmaceutical companies' promotion investment on professional detailing was five times the investment on DTCA (82% vs 18% weight), in 2013 (Cegedim, 2014).

As covered previously, DTCA can have an impact not only on patients' behaviors (increasing the number of requests for drugs subject to DTCA, and the number of visits to doctors, whose effect is positive and long-term), but also physicians prescription behavior (influencing physicians' drug choices to some extent). Research has also shown that DTCA can lead to category expansion and a sales increase of the drug subject to DTCA.

Stremersch & Lemmens (2009) found that countries prohibiting DTCA have significantly lower sales on new drugs when compared to countries where DTCA is allowed, and that this negative effect seems to be more noticeable for newly launched drugs than for maturing drugs. They found that this impact appears to be more intense around one year after a new drug in launched. These findings may contribute to generating insights on how a potential policy restriction on DTCA may impact the sales of new drugs.

6.4.5. Regulation of marketing efforts to physicians

Pharmaceutical companies marketing investments may represent twice the investment made on research and development (Gagnon & Lexchin, 2008).

By the one hand, pharmaceutical companies' associations have been trying to demonstrate the benefits of pharmaceutical marketing. An example of the former can be seen in the Pharmaceutical Research and Manufacturers of America (PhRMA) report issued in 2008, called Pharmaceutical Marketing in Perspective, where, as covered before, it defended the pharmaceutical manufacturers' perspective on pharmaceutical marketing. By the other hand, regulators have been developing initiatives to limit the marketing efforts to health care professionals and institutions, which can be classified into three subgroups, according to Stremersch & Lemmens (2009): constraining the number of detailing visits a pharmaceutical company can make; constraining the number of meetings a pharmaceutical company can organize; or constraining the number of samples a pharmaceutical company can dispense. They pointed some countries where marketing restriction policies had already been implemented, such as the UK, Spain, and Poland.

Research conducted by Stremersch & Lemmens (2009) evidenced that marketing efforts appear to be lower in countries with marketing efforts restriction (Belgium and UK) than in countries without those marketing efforts restrictions (US, Germany and Switzerland). They also found that the impact of restricting pharmaceutical marketing efforts firms develop with physicians tends to have a negative effect on sales (illustrated in figure 6.3).

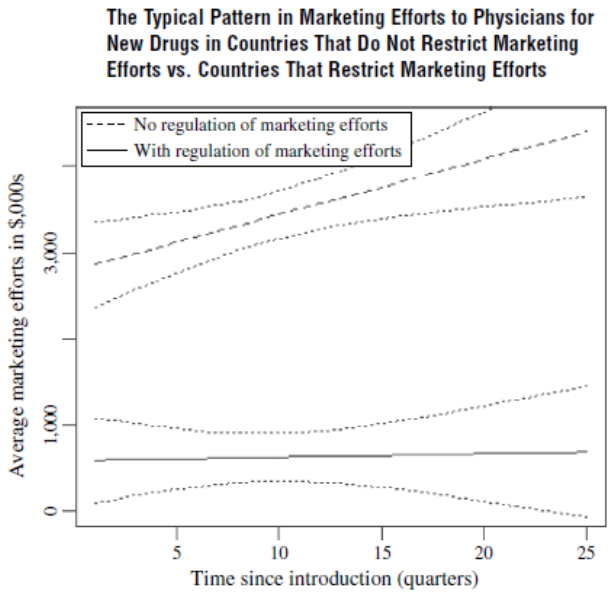


Figure 6.3 - Pattern of marketing efforts to physicians vs time since medicine introduction

Source: Stremersch & Lemmens (2009)

As seen above, Stremersch & Lemmens (2009) addressed some pharmaceutical promotion restrictions subgroups, consisting of direct-to-consumer advertising, restrictions on the

number of detailing visits, restrictions on the number of meetings, restrictions on number of samples, restrictions on marketing / promotion efforts, and restrictions on promotion (proportion of sales). Brennan et al (2006) and Grande (2009) had also addressed restrictions on gifts offered to physicians, and Grande (2009) addressed licensing of pharmaceutical sales representatives.

In order to more deeply approach restrictions on pharmaceutical promotion, we selected seven countries for comparison: France, Italy, Germany, Spain, UK, Portugal and the USA. The reason for this country perimeter was to include the big five European countries, the USA as the country with most research in the field of pharmaceutical marketing, and Portugal, as the country where the empirical component of the thesis will be developed. Data sources were previous work developed by scholars, a non-exhaustive analysis of national legislations, and analysis of legislation compendiums from Baker Mckenzie (2016) and Thomson Reuters Practical Law (2017).

Restrictions on gifts

All the six selected European countries have implemented restrictions on gifts. For instance, in the **UK**, inexpensive gifts are those up to £6 + VAT and may include pens, notepads, calculators, computer accessories, diaries, calendars, surgical gloves, tissues and coffee cups (this limit can increase to £130 in special situations, including books, training material, journal subscriptions, and other).

In **France**, gifts to health care professionals are considered acceptable when simultaneously directly related to the practice of medicine or pharmacy, and of negligible value, up to €30 + VAT, per health care professional, per year.

In **Portugal**, professionals can be given gifts up to €60, above which disclosure to the public must be made (in an INFARMED platform called Placotrans), according to Order 20/2013 of February the 14th, later precised by Decree-Law 5/2017 of January the 6th (eliminating the double registry of benefits, both from entities offering the benefits, and from the recipients of benefits). The 60€ limit was set by Order 12284/2014 of October the 6th, and then revoked by Order 1542/2017, of February the 15th, which defined the concept of objects of insignificant value to the practice of health professionals (60€).

In **Italy**, legislation demands that gifts can only be of modest value, not explicating however what the definition of "modest value" is, and in **Spain** gifts can be given to physicians when

three conditions are observed: their value does not exceed €60, the materials are relevant to the doctors' practices, and they can benefit the patient. In Germany, as expressed in Thomson Reuters Practical Law (2017) compendium, both the Advertisement of Healthcare Products Act (Heilmittelwerbegesetz) (HWG) and industry guidelines prohibit the offering of gifts except they are inexpensive and relevant to the practice of human medicine, and following FSA guidelines gifts are considered as "inexpensive" if their purchase price is up to EUR5.

Restrictions on drug samples

Also, all six European countries have set restrictions on free drug samples offered to physicians. In the **UK** and **France**, no more than four drug samples per particular medicine can be given to physicians, during the course of one year. In **Portugal**, the maximum number of samples for a specific medicine is twelve per year, per doctor, but only in the first two years after the commercialization of the medicine (Deliberation nr. 44/CD/2008, of 7th February). In **Italy**, physicians can receive up to eight samples of a drug, in the first 18 months after the first marketing of a product, at a maximum of two samples per visit. In **Spain**, physicians can be given a maximum of 10 samples of a product per year, per physician, but only during the first two years from the date of authorization. In **Germany**, the limit is two samples per year, per medicine, per doctor.

Restrictions on DTCA, marketing expenditures, number of visits (detailing) and meetings, and PSR licensing / accreditation

Direct-to-consumer advertising is forbidden in all six European countries selected for analysis. Based on the legislation and compendiums analysis, only two of the countries selected for analysis have implemented restrictions on PSRs visits to physicians. These are Portugal, under Order 8213-B/2013, 24th June (which entered into force on August the 1st 2013), and Spain, where limits can be imposed in some of the autonomous regions. In Portugal, limits on detailing were set for PSRs access to the NHS institutions and physicians (with a maximum of two PSRs per day in Hospital services, or three PSRs per day in other NHS settings; a maximum of eight visits per day per PSR; a maximum of six visits per year, per company to NHS, or eight visits, subject to special procedures and requests). In Spain, according to Baker Mckenzie (2016), some regions established a maximum number of visits per pharmaceutical manufacturer, per year, or established specific days and hours when PSRs visits are permitted. These restrictions are called detailing ceilings, as explained by Liu et al (2016). They defined detailing ceilings as a limitation placed on the number of detailing visits

for a drug, which can be made to a physician, within a certain period of time. Baker Mckenzie (2016) also explicated that some regions in Spain demand that sales calls from PSRs must be made to a panel of doctors (collective calls). In the USA, some academic medical centers have implemented policies to limit the access of PSRs to doctors, with the goal of reducing the influence of detailing on prescription behavior.

Larkin, Ang, Avorn & Kesselheim (2014) noted that some health institutions such as academic medical centers restrict detailing activities with the goal of reducing the impact of this promotion tool on physicians' prescription behavior. They studied the impact of restriction of detailing activities in academic medical centers in the scope of antidepressants and antipsychotics in children, and found that, after the entry into force of the detailing restriction policies, on-label prescriptions of promoted drugs dropped by 34 percent; off-label prescriptions of promoted drugs dropped by 11 percent; on-label prescriptions of nonpromoted drugs rose by 14 percent; and off-label prescriptions of nonpromoted drugs rose by 35 percent. They concluded that PSRs «*promoted drugs not approved for pediatric use and that policies that restrict detailing by those representatives reduced such off-label prescribing*» (p. 1014).

A recent study conducted by Larkin et al (2017) analyzed the impact of these restrictions using a difference in difference multivariate regression model, to compare changes before and after the entry into force of the detailing restriction policy, in five states (California, Illinois, Massachusetts, Pennsylvania, and New York), using an intervention group (composed of physicians who were affected by the detailing restrictions), and a matched control group (composed of physicians not impacted by a detailing restriction policy). Analyzing data from 2006 to 2012, Larkin et al (2017) found that detailing restriction policies had a significant impact on physician prescription behavior in six of the eight drug classes of the drug classes studied. They found that, on average, there was a 1,67 percentage points drop in the market share of the detailed drugs, and a 0,84 percentage points increase in the market share of non-detailed drugs. They also found that these changes were observed in eight of the 11 academic medical centers whose data was used in the research. Larkin et al (2017) concluded that the «*implementation of policies at AMCs that restricted pharmaceutical detailing between 2006 and 2012 was associated with modest but significant reductions in prescribing of detailed drugs across 6 of 8 major drug classes*» (p. 1785).

Another recent research was developed by Liu, Liu & Chintagunta (2017), using simulated potential regulation limiting the number of detailing visits per month to a ceiling of one.

Contrary to what policy makers intend when they set detailing restrictions to reduce pharmaceutical expenditures and encourage generics prescriptions in opposition to more expensive drugs under patent, they found that a detailing ceiling in the scope of combination therapies using generics benefiting from spillover effects from the focal (promoted drug) may have unplanned effects, by reducing the number of generics prescriptions.

Liu et al (2016)'s counterfactual simulations on the effect of several detailing ceilings suggested that a detailing ceiling may impact competing brands' detailing elasticities differently, moderating them. By other words, a detailing restriction policy could attenuate the positive effect of the detailing impact on prescription behavior for the drug with the highest detailing intensity, and the opposite for the drugs with lower detailing intensities, as illustrated in figure 6.4 below.

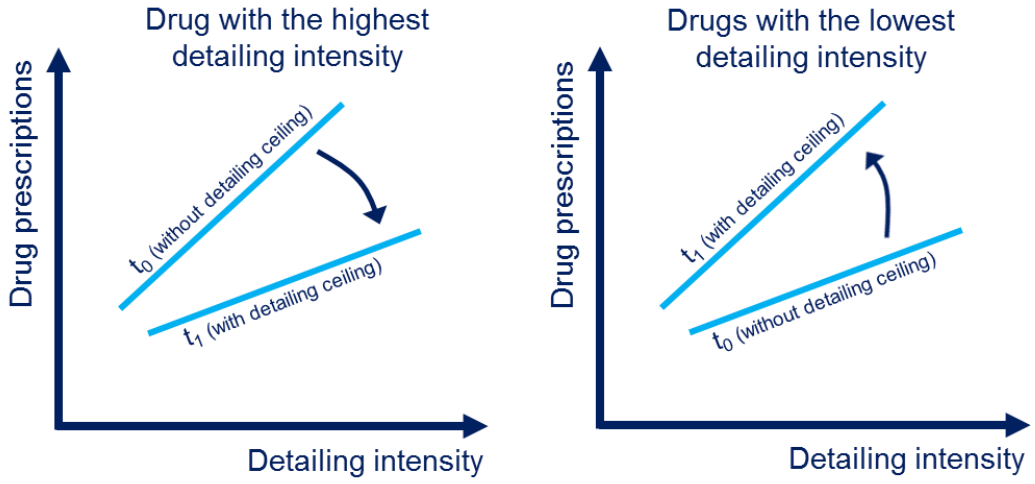


Figure 6.4 – Expected impact of a detailing ceiling on detailing flow elasticity

Source: own elaboration based on Liu et al (2016)

Liu et al (2016) estimated that, under a detailing restriction policy, detailing leaders will suffer the highest reduction in share of voice and market share, and drug brands with lower detailing frequency will increase their share of voice and market share.

Limits on the number of meetings organized were not identified considering the selected country perimeter. Limits on the global marketing / promotion efforts have been implemented in the UK and in Spain, as noted by Stremersch & Lemmens (2009). In the UK, marketing investments cannot be higher than a percentage of profits (as a marketing allowance), and in Spain, promotion investments cannot be higher than a percentage of sales. Several countries have also implemented licensing or accreditation of PSRs. In the **USA**, the National

Association of Pharmaceutical Sales Representatives (NAPSR) created a Certified National Sales Representative (CNSR) certification, which can be given in partnership with some colleges and universities. This certification, despite not being compulsory yet, may become rapidly a condition to access the PSR profession (Alkhateeb et al, 2011). In **Spain**, as underlined by Thomson Reuters Practical Law (2017) in their compendium of legislation on marketing of prescription drugs, PSRs must receive adequate training and sufficient scientific knowledge. In the **UK**, PSRs must receive full training so that they can promote medical products to prescribers. In **Italy**, a scientific service from each marketing authorization holder must verify that their PSRs have received adequate training and perform according to the regulations. In **Portugal**, article 156 from decree-law 176/2006 (30th August) foresees that pharmaceutical manufacturers must ensure that PSRs promoting medicines on their behalf have the appropriate qualifications and professional training necessary for the full performance of their duties, exercising their profession in full compliance with their obligations. PSRs accreditation is obtained when the marketing authorization holders register their PSRs in INFARMED.

Combining the theoretical and regulation grounding, table 6.1 was developed highlighting its applicability in the selected perimeter of countries, whose goal is to analyze the extent to which each country has implemented restrictions in some or several promotion practices, to better frame the Portuguese reality.

Table 6.1 – Restriction on promotion activities in a selected group of countries

	Theoretical grounding of restriction instrument / Regulation grounding (Global: Directive 2001/83/EC)	DTCA prohibition	Limits on global marketing / promotion efforts	Limits on the number of visits (detailing)	Limits on number of meetings organized	Limits on number of samples provided	Prohibition of gifts non-relevant to the practice of medicine (of unreasonable value)	Compulsory licencing / obligation of accreditation / specific training of pharmaceutical sales reps[1]
		(Stremersch & Lemmens, 2009)	(Stremersch & Lemmens, 2009)	(Brotzman & Mark, 1992; Brotzman & Mark, 1993; Stremersch & Lemmens, 2009; Stremersch & Van Dyck, 2009; Liu, Gupta, Venkataraman & Liu, 2016; Larkin et al, 2017)	(Stremersch & Lemmens, 2009)	(Brennan et al, 2006; Stremersch & Lemmens, 2009)	(Brennan et al, 2006; Grande, 2009)	(Grande, 2009)
France	French Code of Public Health (FCPH)	Yes[2]	No	No	No	Yes	Yes[3]	N/A
Italy	Legislative Decree 24th April 2016 | Community Code of Medicinal products of human use | Farmindustria Ethics Code	Yes	No	No	No	Yes	Yes	Yes
Germany	Advertisement of Healthcare Products Act | Act Against Unfair Competition | Medicinal Products Act	Yes	No	No	No	Yes	Yes	N/A
Portugal	Legal Regime of Medicines for Human Use (Decree Law 176/2006, 30th August | Order 8213–B/2013	Yes	No	Yes	No	Yes	Yes	Yes
Spain	Law on Guarantees and Rational Use of Medicines and Medical Devices (Medicines Law) | Royal Decree 1416/1994	Yes	Yes	Yes[4]	No	Yes	Yes	Yes
UK	Human Medicines Regulations 2012 (Regulations 294 to 300)	Yes	Yes	No	No	Yes	Yes	Yes
US	Food and Drug Administration (FDA) | Office of Prescription Drug Promotion (OPDP) | Advertising and Promotional Labelling Branch (APLB) | PhRMA code with voluntary limits on detailing	No	No	Yes[5]	No	No	No	Yes

Notes: 1) By company or manufacturer association; 2) exception of campaigns for vaccination against human infectious diseases, subject to prior authorization;
3) Gifts with a value up to €60 are considered of reasonable amount, and not subject to the anti-gift law; 4) In some autonomous regions; N/A - information not located; 5) Some academic medical centers have implemented restrictions on PSR access

Source: own elaboration

Prevalence of restriction policies

Brotzman & Mark (1992) developed research to determine the prevalence of policies restricting or regulating the interactions of PSRs with family medicine doctors, trying to assess to which extent certain restrictions were present in residency programs. The restrictions they evaluated were restrictions or limitations on: contact during working hours, on clinic drug samples, on personal samples for residents, on displays, on distribution of literature, on gifts and outings, and on group presentations. They found that, globally, residency programs permitted most of the activities, with the exception of informal guidelines concerning interactions with PSRs, concluding that the sample evidenced substantial variation regarding regulation of PSRs and doctors' interactions.

One year later, Brotzman & Mark (1993) studied the effect of regulatory policies regarding PSRs activities on residents' attitudes. They found some very interesting results: residents working at healthcare institutions without restrictions on PSRs' activities were four times more likely to view PSRs detailing activities as helpful, when compared to residents working at healthcare institutions where restrictions were into force. They also found that doctors from restricted programs declared a substantially lower number of contacts with PSRs, versus doctors from non-restricted programs, suggesting, as a possible explanation, that the absence of restrictions in some programs may be interpreted as a favorable disposition, from program directors, to PSRs activities.

Brennan et al (2006) proposed a policy for Academic Medical Centers to eliminate conflicts of interest between physicians and the healthcare industry, by removing or modifying practices such as small gifts, drug samples, CME, funds for travel and accommodation, and consulting. Wazana (2000) had already questioned the lack of guidelines concerning resident and pharmaceutical industry representatives' interactions or the efficacy of the existing guidelines.

Disclosure of pharmaceutical manufacturers marketing interactions with physicians

National legislations have been increasingly demanding pharmaceutical companies to disclose transfers of value to HCPs and HCOs. This has been seen in countries such as the USA with the Sunshine Act implementation in 2012, taking full effect in September 2013, as noted by Liu et al (2016). Pharmaceutical companies started reporting payments made to physicians, in a public database, as noted by Karas et al (2016), being 2014 the first full year where transfers of value made to physicians and teaching hospitals were disclosed. Australia had already

implemented a similar program, in 2007, where the Australian Competition Tribunal placed disclosure requirements on Medicines Australia, the Australian pharmaceutical industry representative association. A Code of Conduct for industry–professional relationships was created, and details of every sponsored event, including the costs of any hospitality, were publicly posted on a website (Robertson, Moynihan, Walkom, Bero & Henry, 2009).

In 2011, French Ministry of Health published its own Sunshine Act, Decree number 2013-414, a law known as Bertrand Law, demanding disclosure of not only direct payments and grants, but also indirect payments (for instance, when a pharmaceutical company pays a hotel for the physicians' accommodation). The French legislation goes also further by including additional eligible institutional recipients other than hospitals and teaching hospitals, such as Associations, Foundations, editors of prescription software, and also eligible individual recipients other than physicians, such as nurses, pharmacists, dentists, medical students and other).

In Portugal, the Ministry of Health implemented new legislation in 2014 (Dispatch 12284/2014, which defined the EUR60 threshold, précising Decree Law 176/2006 (30th August)' concept of gift of insignificant value), demanding pharmaceutical companies to disclose transfers of value higher than EUR60 to healthcare professionals and healthcare organizations. The disclosure must be made using a specific INFARMED website called PLACOTRANS, with on-line available information for general public access. There seems to be nevertheless a delicate balance between the need for disclosure and transparency, and the need to guarantee recipients' privacy. Vitry (2016) noted that Medicines Australia's Code of Conduct includes an opt-out option, where healthcare professionals can choose not to have their name publicly reported in the disclosure of transfers of value such as advisory board fees, speaking fees, and other transfers of value. EFPIA code in Europe also includes an opt-out option, where recipients must authorize the disclosure of transfers of value, or at a minimum must have the opportunity to opt-out of disclosures.

Table 6.2 summarizes the codes and legislation backgrounds from seven countries, regarding disclosure of transfers of value to healthcare practitioners and organizations. It was built based on the International Comparative Legal Guides (ICLG, 2017), data compiled by Global Legal Group, an organization specialized in comparative legal analysis, and on previous research conducted by scholars publishing in these fields.

Table 6.2 – Comparative analysis of codes and legal grounding on disclosure of transfers of value

	Disclosure of transfers of value to health care practitioners (HCPs) and health care organizations (HCOs)			
	Industry Associations codes		National legislation / Procedures	Theoretical grounding (non-exhaustive)
	International	National		
France	EFPIA Code	Leem Code	Public Health Code (articles L. 1453-1 from Bertrand Law)	(Karas, Bandari, Browning, Jacobs & Davies, 2016; Liu, Gupta, Venkataraman & Liu, 2016)
Italy		Farmindustria Code	No specific legislation	
Germany		VFA (FSA Code)	Law on advertising in the field of healthcare	
Portugal		Apifarma Code	Dispatch 12284/2014 + Decree Law 176/2006 (30th October) | Placotrans platform (Infarmed)	
Spain		Farma Industria Code	No specific legislation	
UK		ABPI Code	No specific legislation	
USA	---	PhRMA Code	Physician Payments Sunshine Act	

Source: own elaboration

As highlighted by Liu et al (2016), the transparency requirements impelled «*physician practices and hospitals to severely restrict pharmaceutical sales representatives' direct access to their physicians*» (p. 1). However, as noted by Loewenstein, Sah & Cain (2012), disclosure of conflicts of interests – both financial and non-financial -, despite positive and necessary, can lead physicians to provide biased advice to patients and is likely to increase pressure to take the physicians' advice, despite a decrease in trust (due to patients' fear of revealing lack of trust in the doctors). Loewenstein, Sah & Cain (2012) ended their article by suggesting policies to increase the effectiveness of the disclosure of physicians' conflicts of interest. These include unconflicted second opinions (even covered by health insurers), and the creation of a unified internet-based universal online disclosure form. They ended by underlining that one of the greater limitations of disclosure is the moral licensing, which they define as «*the rationalization that, with disclosure, the profession has dispensed with its obligation to deal with conflicts of interest*» (p. 670).

6.5.Regulation effectiveness

Several scholars have been discussing the effectiveness of both self and government regulation in the scope of the pharmaceutical industry marketing initiatives. Grande (2009), in his discussion on self-regulation versus government intervention on pharmaceutical industry gifts and detailing to physicians, suggested that while the governmental regulation and actions are needed, the «*medical profession needs to reclaim its independence from industry*» (p. 82), and that «*regulation alone can't fully address the negative influences of marketing*» (p. 82). Herxheimer & Collier (1990) noted that the Association of the British Pharmaceutical Industry (ABPI) developed its code of practice in order to auto regulate the promotion of prescription medicines. Their research concluded that the ABPI code did not reveal an obvious deterrent effect regarding non-compliant promotion activities. Herxheimer & Collier (1990) suggested that proper compulsory intervention from the health ministers would be necessary to regulate pharmaceutical manufacturers' promotion activities. Despite the voluntary compliance of pharmaceutical manufacturer associations' codes of conduct, research has demonstrated that some breaches might exist, when applying those codes. The main issue is that standards to observe by manufacturers are determined by the industry (Herxheimer & Collier, 1990), which might involve some tension between the commercial and ethical foundations of these codes and lead to weaknesses in their applications (Lexchin, 1997).

Norris, Herxheimer, Lexchin & Mansfield (2005) concluded, in their review on drug promotion by pharmaceutical companies, that there are effective and ineffective interventions to counter promotion activities. The effective initiatives are government regulation of promotion (more effective than industry self-regulation), educating doctors about drug promotion (which influences attitudes and can improve skills), and publication of deceptive promotion. Ineffective initiatives are pharmaceutical industry self-regulation, review by journal editors, guidelines/regulations for sales representatives or for advertisements, and government control of post-marketing surveillance. Disclosure of marketing investments by manufacturers may not be as effective as tutelage compulsory bans in terms of prescription reduction, as noted by King & Bearman (2017). They also found that the uptake of new expensive medications was significantly lower in US states with government marketing regulation, when compared to states allowing unrestricted pharmaceutical marketing. Figure 6.5 illustrates the main interventions and institutions in the scope of regulation of pharmaceutical marketing.

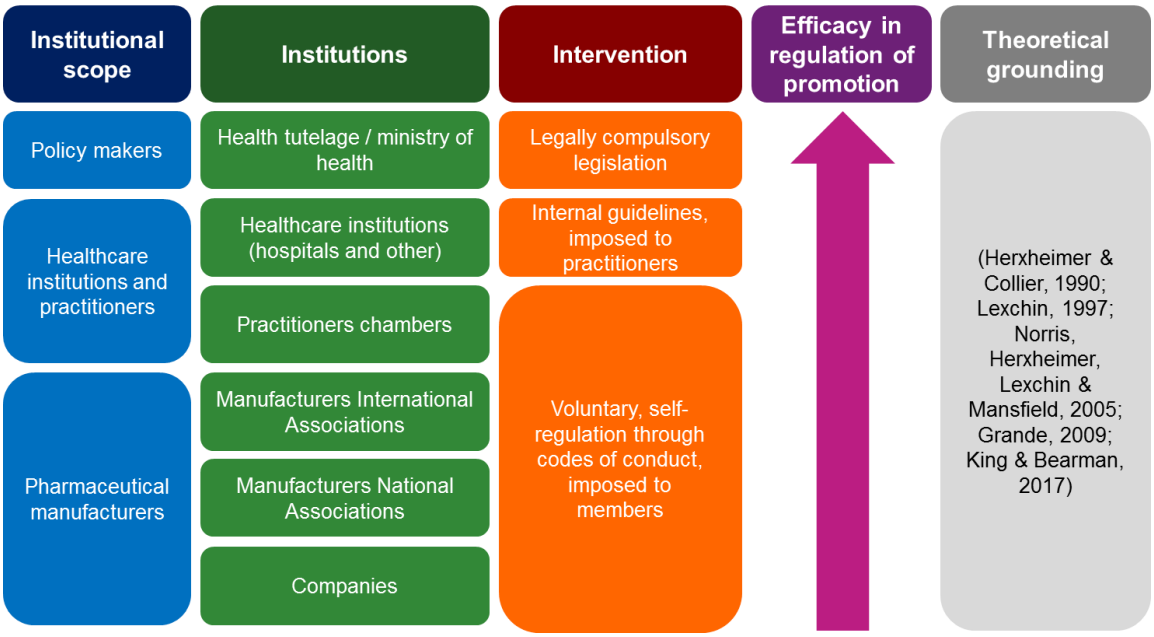


Figure 6.5 – Summary of main interventions to regulate pharmaceutical marketing

Source: own elaboration

Recognizing the scant literature on the impact of detailing restriction policies on prescription behavior, and given that manufacturers are increasingly facing difficulties in accessing physicians due to either government regulation, pharmaceutical manufacturers associations, or by physicians and their practices, Liu et al (2016) studied the effectiveness of several scenarios of simulated detailing restriction policies (detailing ceilings), to shed light on the implications for competing firms. They conducted research using data collected by a market research firm operating in the EUA, from a panel of physicians. Each physician reported the number of calls (visits received by PSRs) and the number of prescriptions for each drug included in the research perimeter (three drugs plus one non-drug treatment, in the statins class), and the time series included data from 24 months. Using a structural model, Liu et al (2016) simulated two different detailing restriction scenarios: one imposing a maximum of one visit per month, and one imposing a maximum of one visit per quarter. They reached very interesting conclusions: detailing restriction policies lead to reduced levels of detailing and expand prescription option that do not rely on detailing (in the case, detailing restriction policies would benefit the nondrug, non-detailed treatment-only option); with ceiling policies, the drug with the largest detailing stock effect and the highest detailing frequency suffer the most (market share and profit decreases), that is, firms that rely more on detailing would lose proportionally more market share; the stricter the detailing ceiling, the more the benefits to firms with weaker detailing effects, meaning that a detailing restriction policy would tamper

detailing competition between the firms, and increase their profits (since the reduction in market share would be more than compensated by a lower burden of PSRs costs); competitors raise their detailing levels and do not imitate individual firms in terms of limiting their own detailing levels, since the latter would lose profits, and the former would enjoy a profit gain, meaning that, to be effective, the detailing restriction policy must be imposed to all firms competing in the market.

Larkin, Ang, Avorn & Kesselheim (2014) studied the impact of restriction of detailing activities in academic medical centers in the scope of antidepressants and antipsychotics in children, and found that, after the detailing restrictions, on-label prescriptions of promoted drugs dropped by 34 percentand on-label prescriptions of nonpromoted drugs rose by 14 percent. Three years later, Larkin et al (2017), studied the effect of detailing restriction policies on physician prescription behavior on 11 academic medical centers (before and after the entry into force of detailing restriction), and reached conclusions that are similar to the ones obtained by Liu et al (2016): detailing restriction policies had a significant impact on physician prescription behavior in six of the eight drug classes of the drug classes studied, where on average there was a 1,67 percentage points drop in the market share of the detailed drugs, and a 0,84 percentage points increase in the market share of non-detailed drugs. To the best of our knowledge, these two articles are the first using real data on the effect of detailing restriction policies, and not counterfactual simulations. Figure 6.6 below demonstrates the effects of the detailing restrictions on drugs market share. The reduction in market share of detailed drugs is stronger in the case of drugs unaffected by generic entry.

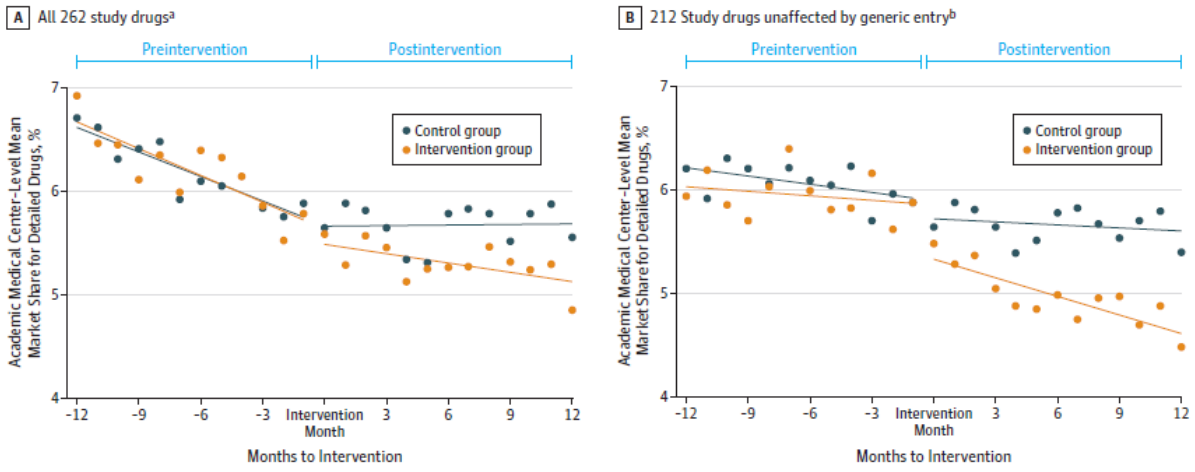


Figure 6.6 – Larkin et al (2017) mean market share of detailed drugs

Source: Larkin et al (2017)

6.6.Chapter synthesis of main findings

This chapter covered regulation on pharmaceutical manufacturers' marketing practices (mainly promotion) on physicians and health care organizations. It started by addressing self-regulation, exploring pharmaceutical manufacturers, pharmaceutical manufacturers associations, physician chambers, and healthcare organizations initiatives to auto-regulate the interactions between manufacturers and physicians. The literature has shown, however, that these types of initiatives have little to no effect as an instrument to regulate pharmaceutical promotion.

The chapter also covered government regulation of pharmaceutical marketing, exploring manufacturer price regulation, regulation on physician prescription budgets, patient payment policies, regulation of direct-to-consumer advertising, and most importantly to the scope of this thesis, regulation of marketing efforts to physicians. Previous literature has shown that compulsory restrictions on pharmaceutical marketing are much more effective than self-imposed ones, as interventions to counter promotion activities. Table 6.3 summarizes the main effects of these government restrictions on pharmaceutical marketing activities.

Table 6.3 – Summary of the effects of government regulation of pharmaceutical marketing

	Scope	Brief description	Effect	Theoretical grounding of the effect	Other theoretical grounding (non-exhaustive)
Government regulation	**Government regulation**	Government has direct control of the manufacturer drug price	Price control can cause launch delays | Drug sales tend to be higher in countries with manufacturer price control	Stremersch & Lemmens (2009(	(Danzon, Wang & Wang, 2005; Kyle, 2007; Golec & Vernon, 2010)
	Regulation on physician prescription budget	Government limits the total number of prescriptions a physician can write	Negative effect on drug sales (more effective for mature drugs than for new drugs)		(Granlund, Rudholmand & Wikstrom, 2006; Andersson, Petzold, Allebeck & Carlsten, 2008; Fischer, Koch, Kostev & Stargardt, 2017)
	Patient co-payment regulation	Patients are requested to provide some form of co-payment for prescription drugs	Negative effect on drug sales		(Reuveni et al, 2002; Luiza et al, 2015)
	Regulation of Direct-to-consumer advertising (DTCA)	Government prohibition of direct-to-consumer advertising (set by all countries except USA and New Zealand)	Negative effect on new drug sales		(Stremersch & Lemmens, 2009)
	Regulation on marketing efforts to physicians	Government restriction on the number of detailing visits a manufacturer can make, the number of meetings a manufacturer can organize, or the number of samples a manufacturer can dispense to physicians	Negative effect on drug sales (altough non-significant for the countries analyzed)		(Brotzman & Mark, 1992; Brotzman & Mark, 1993; Wazana, 2000; Brennan et al, 2006; Liu, Gupta, Venkataraman & Liu, 2016; Karas, Bandari, Browning, Jacobs & Davies, 2016; Larkin et al, 2017)

Source: own elaboration

Regulation of marketing efforts to physicians can take form of restrictions on gifts, on drug samples, on DTCA, on marketing expenditures, on the number of visits and meetings, and on PSR licensing / accreditation. The literature and legislation analysis of seven countries allowed to recognize that, despite some differences, the six European countries selected evidence reasonably similar restrictions regarding gifts and drug samples (the extent of which do however vary a little). The UK and Spain imposed limits on marketing / promotion expenditures as a percentage of the profits (in the first) or of the sales (in the second). Among these six European countries, Portugal seems to be the only with national legislation that limits PSRs' access to physicians and institutions of the NHS. Spain does appear to have some restrictions in this scope, but only in some regions.

The chapter ended by exploring very recent research on pharmaceutical promotion restrictions – specifically on detailing restrictions, developed by Liu et al (2016) with counterfactual simulations, after collecting data from a panel of physicians practicing in the USA (prescription and detailing data). Based on their simulations where detailing ceilings were tested, they obtained very interesting findings, here summarized below in table 6.4.

Table 6.4 – Theorized effects of detailing restriction policies

	Theorized effects	Theoretical grounding
Detailing ceiling	Detailing restriction policies leads to reduced levels of detailing and expands prescription option that do not rely on detailing	(Larkin, Ang, Avorn & Kesselheim, 2014; Liu, Gupta, Venkataraman & Liu, 2016; Larkin et al, 2017)
	With ceiling policies, the drug with the largest detailing stock effect and the highest detailing frequency suffers the most (market share and profit decreases)	(Liu, Gupta, Venkataraman & Liu, 2016)
	The stricter the ceiling, the more the benefits to firms with weaker detailing effects | Detailing ceilings soften detailing competition	(Liu, Gupta, Venkataraman & Liu, 2016)
	Competitors raise their detailing levels and do not imitate individual firms in terms of limiting its own detailing levels. The later loses profits and the former enjoy a profit gain	
	Implementation of policies at academic medical centers that restricted pharmaceutical detailing may be associated with modest but significant reductions in prescribing of detailed drugs	(Larkin, Ang, Avorn & Kesselheim, 2014; Larkin et al, 2017)
	Detailing ceilings under combination therapies using generics can potentially hurt generics	Liu, Liu & Chintagunta (2017)

Source: own elaboration

7. Conceptual model

In the scope of the current thesis, we developed a literature review on the lifesciences industry, pharmaceutlcal marketing, and regulation and policy of pharmaceutical marketing. The literature was then organized in order to address the effect of pharmaceutical industry promotion initiatives on physicians' prescription behavior, moderated by policy regulation on pharmaceutical promotion initiatives (specifically detailing). This was performed to identify the conceptual framework (Creswell, 2014) of the proposed research.

The literature review performed allowed the understanding that detailing – a form of personal selling (Fischer & Albers, 2010) and a form of relational marketing (Gronroos, 1994) - involves direct visits from PSRs to individual doctors, during which PSRs provide information about their company's drugs, free samples, scientific literature, trying to combat the efforts of PSRs from competing companies (Rao & Yamada, 1988; Steinman, Harper, Chren, Landefeld & Bero, 2007). It is not only the most used promotion tool (Yi, Anandalingamb & Sorrell, 2003; Gagnon & Lexchin, 2008; Datta & Dave, 2016), but also the tool with a higher effect on physicians' prescribing behavior (Pitt & Nel, 1988; Berndt, Bui, Reiley & Urban, 1995; Narayanan et al, 2003; Narayanan, Desiraju & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kalyanaram, 2008; Kalyanaram, 2009; Dave & Saffer, 2012).

Evidence from the theory suggests that detailing has a significant and positive effect on prescription behavior translated into an increase in the number of prescriptions of the promoted prescription drug (Stremersch & Van Dyck, 2009; Stremersch & Lemmens, 2009), in a causal relation. Despite the fact that several previous research articles have pointed to different elasticities (or effect magnitudes) of detailing (Kremer et al, 2008; Stremersch & Van Dyck, 2009), the great majority of articles (indluding reviews made by Kremer et al, 2008, and by Spurling et al, 2010) point to a positive effect, with an average elasticity of 0,326. This average was calculated by Kremer et al (2008) in their review, using 252 detailing elasticities.

The theory also suggests that policy measures have been implemented by Governments to regulate pharmaceutical manufactuers' marketing initiatives directed at physicians, which include regulation of marketing efforts to physicians (Stremersch & Lemmens, 2009; Stremersch & Van Dyck, 2009). Despite the scant literature on this specific field, existing evidence suggests that constraining the number of detailing visits a pharmaceutical company

can make can lead to a negative effect on the sales of the promoted drugs (Stremersch & Lemmens, 2009).

This impact may be differentiated among drugs brands, as noted by Liu et al (2016). They estimated that, with a detailing ceiling, the drug with the largest detailing frequency suffers the most in terms of market share and profit decreases, while less detailed brand drugs appear to gain market share and profits. Larkin et al (2014) and Larkin et al (2017) also found that the detailed drugs tend to lose market share under a detailing restriction policy, and non-detailed drugs tend to increase their market share under the detailing restriction policy.

These findings suggest that a detailing ceiling may impact detailing elasticities differently among competing drug brands. The regulation of detailing regulation (in the form of a detailing ceiling) therefore may act as a moderating variable to the effect of detailing on physician prescription behavior.

Consequently, this theoretical pavement allowed the identification of the main variables involved, forming a research hypothesis, which specifies the relationship among variables in terms of direction (Creswell, 2014).

The model includes three sets of variables: the dependent variable is the number of drug prescriptions in DDDs (number of prescriptions written by physicians for the promoted drug, within a certain period of time, representing the promoted drug sales, to evaluate physicians' prescription behavior, and measured as Ln Drug sales in DDD), the independent variable is the detailing intensity (measured as the number of calls (as an office visit with physician contact), in which the promoted drug is detailed, within a certain period of time, and measured as Ln Detailing flow), and the moderating variable is the policy measure consisting of the 2013 detailing ceiling (limitation placed on the number of detailing visits for a drug, that can be made to NHS infrastructure, within a certain period of time).

A visual representation of the conceptual model is presented above, in figure 7.1, adapted from Liu et al (2016)' research.

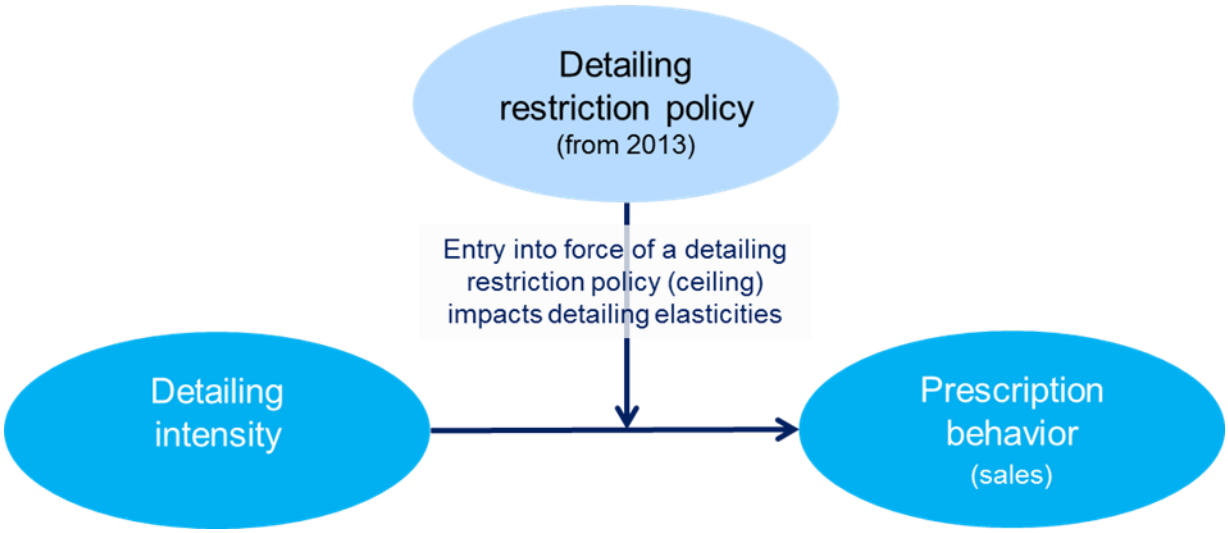


Figure 7.1 – Conceptual model

Source: adapted from Liu et al (2016)

We will now present additional detail to substantiate this concept model, by presenting the descriptive tables of the conceptual model. We start with table 7.1, which evidences the components of the conceptual model.

Table 7.1 – Components of the conceptual model

Component	Component definition	Author(s) addressing the definition (non-exhaustive)	Measures	Author(s) using the measures (non-exhaustive)
Detailing intensity (measured through detailing flow elasticities)	Number of calls (measured as an office visit with physician contact), in which the promoted drug is detailed, within a certain period of time	(Iizuka, 2004; Manchanda, Rossi & Chintagunta, 2004; Liu, Gupta, Venkataraman & Liu, 2016)	Number of calls (Ln Detailing flow)	(Gönül, Carter, Petrova & Srinivasan, 2001; Narayanan, Manchanda & Chintagunta, 2003; Manchanda & Chintagunta, 2004; Mizik & Jacobson, 2004; Manchanda, Rossi & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kalyanaram; 2009; Montoya, Netzer & Jedidi, 2010; Datta & Dave, 2016; Liu, Gupta, Venkataraman & Liu, 2016)
Prescription behavior (measured through drug sales, sell-in, in DDDs)	Sell-in sales (in DDDs) of prescription drugs written by physicians for the promoted drug, within a certain period of time	(Manchanda, Rossi & Chintagunta, 2004; Liu, Gupta, Venkataraman & Liu, 2016)	Drug sales sell-in (Ln Drug sales in DDDs)	
Detailing restriction policy (also know as detailing ceiling)	Limitation placed on the number of detailing visits for a drug, that can be made to a physician, within a certain period of time	(Liu, Gupta, Venkataraman & Liu, 2016)	Existence of a detailing ceiling (Yes / No)	(Liu, Gupta, Venkataraman & Liu, 2016)

Source: own elaboration

These concepts' definitions were based on a compilation of previous research addressing these concepts, conducted by Iizuka (2004), Manchanda, Rossi & Chintagunta (2004), and Liu et al (2016).

Table 7.2, shown below, evidences the relations between the components of the conceptual model.

Table 7.2 – Relations between the components of the conceptual model

Relation	Formulation of the relation	Author(s) addressing the relation (non-exhaustive)	Methods	Obtained results
Detailing impacts physician prescription behavior	Detailing has a positive effect on the sales of the promoted drug	(Gönül, Carter, Petrova & Srinivasan, 2001; Narayanan, Manchanda & Chintagunta, 2003; Manchanda & Chintagunta, 2004; Mizik & Jacobson, 2004; Manchanda, Rossi & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kremer, Bijmolt, Leeflang & Wieringa, 2008; Kalyanaram; 2009; Stremersch & Van Dyck, 2009; Stremersch & Lemmens, 2009; Montoya, Netzer & Jedidi, 2010; Datta & Dave, 2016; Liu, Gupta, Venkataraman & Liu, 2016)	Quantitative analysis using time-series of drug sales and detailing intensity data	Average detailing elasticity = 0.326 (Kremer, Bijmolt, Leeflang & Wieringa, 2008's review)
Regulation of detailing impacts physician prescription behavior	Entry into force of a detailing ceiling has a differentiated effect on drugs sales, depending on their previous detailing intensity	Liu, Gupta, Venkataraman & Liu (2016)	Quantitative analysis using time-series of drug prescriptions and detailing intensity data. Dynamic structural model of oligopoly competition in detailing + Counterfactual simulations on the effect of several detailing ceilings	- With ceiling policies, the drug with the largest detailing intensity suffers the most in terms of market share, whereas competing drugs with lower detailing intensity may gain market share - Detailing ceilings lead to reduced levels of detailing, and expand prescription options that do not rely on detailing

Source: own elaboration

Liu et al (2016) studied the effectiveness of several scenarios of simulated detailing restriction policies, to shed light on the implications for competing firms. They used a dynamic structural model of oligopoly competition in detailing, complemented with counterfactual simulations on the effect of several detailing ceilings, finding that detailing restriction policies lead to reduced levels of detailing and expand prescription option that do not rely on detailing; that with detailing ceiling policies, the drug with the largest detailing stock effect and the highest detailing frequency suffers the most (market share and profit decreases); that the stricter the detailing ceiling, the more the benefits to firms with weaker detailing effects.

These findings suggest that a detailing ceiling may impact drug brands detailing elasticities diffently. By other words, the ceiling effects may therefore moderate the detailing elasticities distincltly. Their research – using counterfactual simulations, and not actual data from regulation of detailing intensity - suggests that a detailing restriction policy may attenuate the positive effect of the detailing impact on prescription behavior for the drug with the highest detailing intensity, and the opposite for the drugs with lower detailing intensities, as illustrated in figure 7.2.

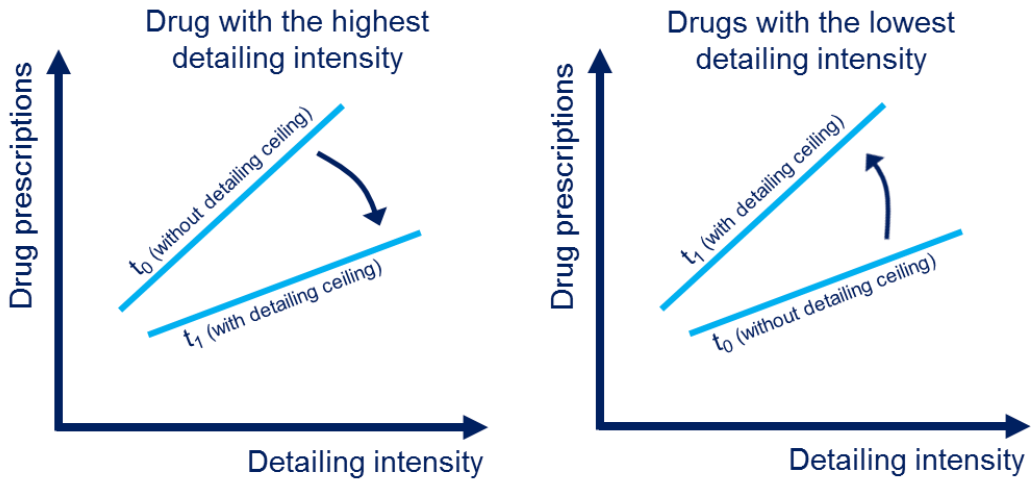


Figure 7.2 – Expected impact of a detailing ceiling on detailing elasticity

Source: own elaboration based on Liu et al (2016)

8. Health care in Portugal

8.1.Content and logic of the chapter

This chapter presents an overview of health care in Portugal. It starts with basic concepts, then presents base notes on health economics in Portugal, approaching the health care infrastructure and health care professionals. Following, the chapter addresses the pharmaceutical market in Portugal, including the pharmaceutical distribution channels, market value, medicines and medicines prices, NHS prescriptions and reimbursments, and generics. It then approaches covers the Portuguuse pharmaceutical legislative background, especially from the years 2000 to 2017, not only underlining legislative initiatives in the scope of prices, reimbursements, and medicines, but also on regulation of PSRs' access to physicians and institutions in the scope of the NHS (detailing ceiling). The chapter then finalizes with a synthesis of the main findings.

This chapter will be mostly a summary of Appendix 2 - Background of economics of health in Portugal, Appendix 3 - The pharmaceutical market in Portugal, and Appendix 4 - Portuguese pharmaceutical legislative framework overview – 2000 to 2017. Therefore, for a deeper analysis of the topics covered in this chapter, please consult these appendices.

8.2.Concepts

This topic will cover basic concepts in the Portuguese health care, with the goal of setting the pavement for the understanding of the specificities of the country in analysis.

Primary, secondary and tertiary care

From a type of care or specialization perspective, there is a distinction between primary, secondary and tertiary care. Primary care represents the first element of the health care process, as a first point of contact of a patient with the health care system. Patients who resort to these healthcare institutions typically are seen by general practitioners of family medicine physicians, seeking treatment for pathologies such as diabetes, respiratory problems (asthma and COPD), back pain, diabetes, and other. Santana & Costa (2008) referred the definition of primary care as «*essential health care based on practical, scientifically sound and socially acceptable methods and technologies made universally accessible to individuals and families in the community through their full participation and at a cost that the community and the country can maintain at each stage development, in the spirit of self-confidence and self-determination. They represent the first level of contact between individuals, the family and the community with the national health system, whereby health care is taken as closely as*

possible to the places where people live and work and are the first element in a continuous process health care» (p. 32).

Secondary care represents the health care services delivered by specialists such as internal medicine specialists, urologists, or cardiologists, who typically do not have first contact with patients (patients are often referred from the primary to the secondary care). Santana & Costa (2008) highlighted that secondary care represents a set of prevention, diagnostic and treatment actions, performed in the acute phase of illness, whose episodes need for specialized interventions, demanding the use of resources with differentiated technology, and are typically provided in hospital units and usually result in short-term episodes. The Portuguese health regulation entity (ERS, 2011) also classified secondary care as hospital care.

Tertiary care represents the advanced or specialized medical treatment, treating diseases such as cancer, or providing health services such as cardiac or neurosurgery. ERS (2011) defined tertiary health care – also known as integrated continuous care – as «*a set of sequential health and / or social support interventions, resulting from a joint evaluation, centered on the global recovery understood as the active and continuous therapeutic and social support process that aims to promote autonomy by improving the functionality of the person in a situation of dependency, through their rehabilitation, rehabilitation and family and social reintegration*».

ERS (2011) defines a fourth type of health care, known as home care, defined as «*the set of activities for prevention, promotion, restoration or maintenance of health, as well as for diagnosis, treatment / therapy and rehabilitation, through a set of resources intended to provide health care to sick or in their homes, homes or institutions*». Typically patients are referred from primary and secondary care to the tertiary care.

Ambulatory and hospital market

The medicines health market can also be classified as ambulatory and hospital. Barros (2014) noted that the main distinction between these two classifications resides in the way the demand is determined. While in the hospital market the patient does not have any participation in the decision making process of medicine choice and there is no patient financial reimbursement of the medicine cost, in the ambulatory market the patient may participate in the choice and may have to pay for part of the medicine retail selling price. Barros (2014) also noted that in the hospital market there is a stronger tradition of using generic medicines. The distinction between hospital and ambulatory can also be made from an infrastructure point of view. While hospital care includes all hospital health infrastructures,

ambulatory care includes all other health infrastructures such as health care centers usually located near residential areas, consisting of the market of medicines that are sold in community pharmacies and other authorized selling infrastructures. The ambulatory health infrastructure network is aimed at preventing and treating patient health issues with a higher proximity to the needed populations, minimizing the necessity for hospital admission. Infarmed (2014) defined, in its glossary, ambulatory market as the market consisting of medicines dispensed to outpatients (that is, patients that are not hospitalized), whose perimeter is given by the sum of prescription plus non-prescription medicines prescribed outside a hospital setting.

Inpatients and outpatients

From a patient type perspective, there are inpatients and outpatients. Inpatients are patients who are admitted at a health care infrastructure and stay there for more than 24 hours, occupying a bed. Conversely, outpatients are patients with health issues which do not require hospitalization. Outpatients can be admitted at a hospital and be subject of several health exams (X-rays, blood analysis, medical consultations), but are medically released in the same day. Andrade, Lima, Pereira, Fornara & Bonaiuto (2013) underlined the main differences between in and outpatients: while «*outpatients are theoretically in a healthier condition, are less dependent on medical and nursing care, spend much less time in the health care setting, and have less contact with doctors, nurses and administrative staff than do inpatients*», inpatients «*stay for at least one night in the hospital, are supposedly in a more delicate condition, and are more dependent on nursing care*» (p. 124).

Prescription and non-prescription drugs

As covered before in the medical prescription topic, the United States Food and Drug Administration (FDA) classifies drugs as prescription and non-prescription (or over-the-counter, or OTC), as underlined by Gabay (2013). Gabay (2013) also noted that a prescription medication, according to the FDA, must be «*dispensed under a valid prescription if, because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug*» (p. 198). On the opposite, non-prescription, or OTC drugs, can be purchased directly at a retail pharmacy, where the term originated, without a prescription (Cooper, 2013). The FDA describes an OTC drug as a

«*medicine that you can buy without a prescription. They are safe and effective when you follow the directions on the label and as directed by your health care professional*» (FDA, 2017a).

In the Portuguese market, only physicians are legally entitled to write a prescription for prescription drugs. OTC medicines can be purchased without a prescription (usually at pharmacies, para-pharmacies or other authorized OTC points of sale). Examples of OTCs include some vitamin supplements, some dermatological lotions and shampoos, some throat lozenges, and other products not demanding a prescription. In Portugal, there are however some specificities regarding OTC medicines. In 2013, a subcategory of OTC was introduced, namely OTC medicines dispensed exclusively in pharmacies (MNSRM-EF), by decree-law 128/2013 (5th September), as noted by Martins, Gonçalves, Marcelo, Vilão & Silva (2016). Examples of this subcategory include acetylsalicylic acid (to treat fever and / or mild to moderate pain in adults and adolescents) and picetoprofen (for cutaneous treatment of mild to moderate pain and inflammation of musculo-skeletal, rheumatic or post-traumatic problems), as stated in Infarmed website as of November 2017. Another specificity sets that there are some OTC medicines that require a prescription from a physician.

Illustrative example of a Portuguese patient

To understand the health care infrastructure and patient treatment process in the Portuguese health care system, an illustrative patient example will now be presented. A patient with a chest discomfort may seek medical advice with his family doctor at the local health center. She has a medical consultation and her doctor refers her to a cardiologist in the regional hospital, whom she visits a week later, and due to the severity of her pathology gets admitted and stays overnight for heart exams and observation. This patient was a primary care outpatient in the ambulatory network infrastructure, and later a secondary care inpatient in the hospital network infrastructure. This patient could then receive high blood pressure drugs prescription, and for instance a non-prescription natural supplement to reduce her stress levels (OTC product).

8.3.Bases on health economics in Portugal

In this sub-chapter, we will present some metrics about Health Economics indicators in Portugal, and their comparison against other European countries.

8.3.1. Brief country overview

According to Pordata (2017), Portugal had, in 2015, a resident population of 10,36 million, almost two thirds of which (65%) concentrated in the age group between 15 and 64 years old, proportion that has been relatively stable since 1981. The extremes of the age pyramid reveal, however, a switch in terms of proportion: while in 1981 there were 2,2 citizens with 15 or less years of age for each citizen with 65 or older, in 2015 this proportion was 0,7 (or 143,9 elders per 100 young people).

The number of births per year has been steadily declining since the eighties, from 213.895 in 1981 to 85.500 in 2015 (Pordata, 2017). In 2011 and 2015 Statistics Portugal data, the number of deaths were higher than the number of births, representing a negative natural population growth.

Gross domestic product in 2016 reached €184.931,1 million, representing an estimated real growth of 1,4% from 2015 (Pordata, 2017). The economy has suffered, since 2005, two main negative impacts: the first one was the 2009 international crisis, provoking a decline of 3% in the GDP in that year; the second was the impact of budget austerity measures imposed by the Troika composed by the International Monetary Fund, European Commission and the Central European Bank, after Portugal's request for budget assistance in April 2011. The austerity resulted in three consecutive years with negative GDP growth rates, reaching – 1,8% in 2011, -4,0% in 2012 and -1,1% in 2013. In 2014 the GDP started to recover, but modestly (+0,9%), and in 2015 and 2016 the growth rate was estimated at 1,6% and 1,4%, respectively (Pordata, 2017).The average growth rate from 2005 to 2016 reached 0,1%, substantially lower than the 1,0% verified in Spain, 3,6% in Ireland, 1,1% in the EU28, and 0,9% in the EU19 Euro zone.

The current health expenditure in Portugal has been stable in the €15.000 million range, from 2012 to 2015 (Pordata, 2017). Portugal has evidenced a relatively stable proportion of the GDP allocated to health expenditures, in the 8,9% (2015 estimate) to 9,9% (year 2009) range. Comparing Portugal against the southern European countries, the most similar 2015 percentages are evidenced by Spain and Italy. Greece evidences a lower percentage (Troika austerity may have been more severe than in Portugal) and France evidences a higher proportion (in line with Germany's). Portugal evidences a proportion of GDP allocated to health marginally lower than Ireland (another country which requested budget assistance to Troika, in 2010). Relatively to the EU28, Portugal evidences one percentage point less in this indicator (OECD, 2016b).

Public administrations have historically been the main contributor to the current health expenditures in Portugal, reaching a proportion of almost two thirds in 2015 (Pordata, 2017). Private financing has been growing its importance, reaching a 34% weight in 2015. Insurance societies contribution has been growing (from 1,5% in 2000 to 3,7% in 2015), while families' contributions (or out-of-pocket costs, as the family health costs that are not reimbursed by public or private systems or insurance) have been relatively steady in the 27% range from 2013 to 2015.

Pharmaceutical spending per capita (on prescription medicines and self-medication (often referred to as OTC products)) evidenced a peak of $522 in 2009, in Portugal, then decreasing to $399 in 2014 (a reduction of 23,6%). Greece, another country that has requested budget assistance to Troika, also revealed a similar pattern, with a peak of $888 per capita, reaching 2014 with a reduction of 29,1%) (OECD, 2015a).

Analyzing Portugal related data in terms of evolution from 2010 to 2014 (Infarmed, 2015), it is evident a substantial reduction of drug consumption per capita in terms of retail price, especially regarding NHS expenditure (reduction of 39,4%). Despite the reduction in the average reimbursement in the NHS (from 69,9% to 62,5%), the average yearly cost borne by patients (out-of-pocket) also suffered an important reduction (-15,7%).

In terms of health care expenditures allocation by type of provider, hospitals and ambulatory represent the highest weights. These two types of providers have been exhibiting a small, but evident increase in their intensity on the total current health expenditures (PORDATA, 2017).

8.3.2. Health care infrastructure

Portuguese National Health System

The Portuguese National Health System (NHS), created in the year of 1979, is a structure through which the Portuguese State assures the right to health (promotion, prevention and surveillance) to all citizens of Portugal. In terms of infrastructure, the NHS has remained relatively stable since the early 2010's, especially regarding the number of General Hospitals (85 in 2015, according to PORDATA (2017)).

Private sector

The number of private hospitals has been increasing in the last decade, reaching 111 units in 2015, representing a growth of 22% from 2005 (INE, 2017). In 2015 there were four hospitals in public-private partnership.

The number of community pharmacies has been stable since the year 2010, on the 2.880 to 2.900 interval (INE, 2017). The reduction seen from 2012 to 2015 may be related to the economic crisis Portugal suffered, and to the regulatory changes implemented with respect to margins of the distribution channel operators (including pharmacies). The Portuguese National Association of Pharmacies (ANF) has issued a press release in August 2016, stating that there were 549 pharmacies in situation of attachment of assets or insolvency, representing a growth of 132% from December 2012 to July 2016. During this period, the insolvency numbers increased from 61 to 196 pharmacies, and the attachment of assets situations increased from 180 to 363 (ANF, 2016).

8.3.3. Health care professionals

According to Decree-Law 20/2013, number 3, point aaa, 14th of February, a health professional is a person legally entitled to prescribe, dispense or administer medicines, namely physicians, dentists, veterinary doctors, odontologists, pharmacists or nurses.

Physicians are the only professional category which is given the responsibility to prescribe medicines in Portugal (Decree-Law 20/2013, number 3, point fff, 14th of February). Dentists and odontologists are also given to right to prescribe certain medicines. Pharmacists are given the responsibility to dispense medicines prescribed by physicians, and to dispense non-prescription medicines. Nurses are given the responsibility to administer the medicines, especially vaccines (however, pharmacists can also legally administer vaccines, since 2008). The number of physicians in 2015 (48.487) was 34,2% higher than in 2005 (36.138), according to INE (2017). This grow has not been however similar between specialists (+28,4%, from 23.307 to 29.919) and non-specialists (+44,7%, from 13.220 to 18.568). In the same period, the number of nurses increased 40,6% (from 48.155 to 67.730) and the number of pharmacists increased 27,6% (from 9.494 to 12.119). Among the more than 70 specialties and subspecialties, the three most representative in terms of weight are General Practice, Internal Medicine and Pediatrics (INE, 2017). In terms of physician density per 100.000 inhabitants, Portugal ranks second on the list with 443 physicians per 100.000 inhabitants, when considering the five biggest countries, and the countries assisted by Troika in the recent past (Portugal, Greece and Ireland) (OECD, 2016b).

8.4.The pharmaceutical market in Portugal

In this sub-chapter, we will summarize the organization and characterization of the Portuguese pharmaceutical market.

8.4.1. Pharmaceutical distribution channels

The distribution channels of the pharmaceutical industry in Portugal are shown below, in figure 8.1:

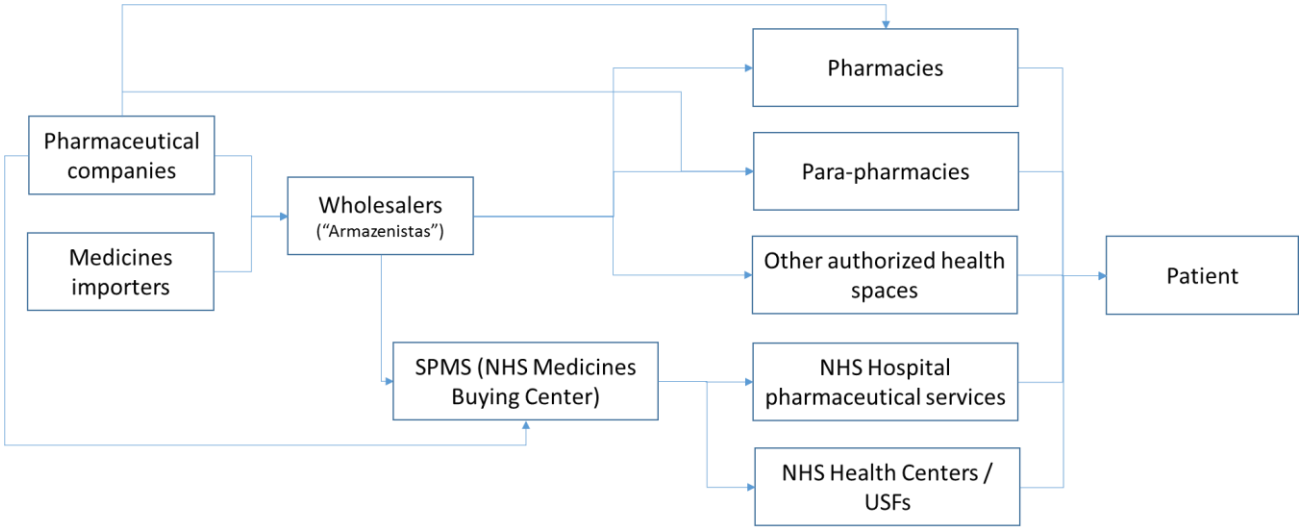


Figure 8.1 - Pharmaceutical industry distribution channel in Portugal

Source: own elaboration

In terms of upstream distribution channel, medicines are either provided by pharmaceutical companies (which can produce the medicines in Portugal or in other country) or by importers of medicines. Wholesalers (called "Armazenistas") by the medicines the pharmaceutical companies, or from importers. Considering the National Health System (NHS) institutions, medicines are bought by a buying center called SPMS (in Portuguese, "Serviços Partilhados do Ministério da Saúde", or Shared services of the Ministry of Health). This buying center will negotiate tenders with wholesalers, or with pharmaceutical companies directly. At a NHS hospital setting, and for patients suffering from chronic diseases eligible for 100% state reimbursement (such as Crohn and ulcerative colitis diseases), patients can collect their medicines (at no cost) at a hospital pharmacy, upon presentation of a medical prescription. In terms of non-NHS hospital settings, pharmacies can buy their medicines from wholesalers (typical situation), or from the pharmaceutical companies directly (less frequent situation). Patients can buy or collect (depending on the reimbursement level) their prescription medicines at community pharmacies, and can buy non-prescription medicines at community pharmacies, parapharmacies and other authorized health spaces (ex: supermarkets such as Pingo Doce, which have small spaces selling over-the-counter medicines).

The number of pharmaceutical companies operating in Portugal has increased from 311 in 2010 to 419 in 419 (this number includes small companies). The number of pharmaceutical companies registered at APIFARMA (the association of the Portuguese pharmaceutical companies, mainly constituted by the large and medium-size companies) has been relatively stable, ranging from 130 in 2010, to 121 in 2015. The number of wholesalers has also been relatively stable, reaching 443 in 2014. As covered previously, the number of pharmacies has been stable too, reaching around 2.900 (the number of pharmacy extensions was slightly below 200 in 2015). The number of drugstores authorized to sell non-prescription (OTC) medicines (constituted by both parapharmacies and small health spaces at commercial areas) reached 1.015 in 2014. Table 8.1 explicits these metrics.

Table 8.1 - Number of companies per distribution channel function in Portugal

Unit: number

	2010	2011	2012	2013	2014	2015
Pharmaceutical companies[(1)]	311	334	367	378	419	---
Pharmaceutical companies associated to APIFARMA[(2)]	130	130	122	121	123	121
Wholesalers[(3)]	402	406	409	409	443	---
Community pharmacies[(4)]	2 879	2 900	2 910	2 881	2 889	2 892
Pharmacy extensions (Posts)[(5)]	176	174	186	184	196	192
Drug stores (authorized to sell non-prescription medicines)[(6)]	915	926	950	1 014	1 015	1 090

Sources: (1) and (3) INFARMED (2015) | (2) and (6) APIFARMA (2016) | (4) and (5) INE (2017)

8.4.2. Pharmaceutical market value

The total medicines market is divided in ambulatory market (prescription and non-prescription medicines), and hospital market (NHS only).

The medicines market evidenced a substantial negative growth from 2010 to 2015 (-16,9%), decreasing from €4.294 million to €3.570 million (APIFARMA, 2016). This decrease was especially evident from 2010 to 2011 (-7%) and from 2011 to 2012 (-9%), the two main years of austerity in Portugal.

In terms of importance (weight on total medicines market), the NHS hospital market has been gaining relevance, growing from 23,9% in 2010 to 29% in 2015 (Apifarma, 2016). This increase has been compensated by a decrease in the ambulatory market importance, especially on the prescription medicines market.

The NHS is the main medicines financier in the Portuguese market. While NHS reimbursement costs decreased from €1.639 million in 2010 to 1.190 million in 2016, a reduction of 27,4%, the out-of-pocket patients' costs remained relatively stable in the €683 million to €799 million range. The non-NHS market comprises sub-systems and the remaining market. The subsystems included the health subsystem of Ministry of Justice, which, in 2011, was transferred to ADSE (Civil Servants Health Care Assistance, or "Assistência na Doença aos Servidores Civis do Estado", in Portuguese. Then, in April 2013, ADSE and other health subsystems belonging to the Clinical and Drug Assistance to the Members of Military and Militarized Forces were incorporated in the NHS. The remaining market includes the market outside the NHS, such as private clinical practice (Apifarma, 2016; Infarmed, 2015; Infarmed, 2017). Table 8.2 provides evidence about these topics.

Table 8.2 - Detailed view of the medicines market – 2010 to 2015 – Portugal – retail price – NHS vs non-NHS

Unit: € Million (retail price)

				2010	2011	2012	2013	2014	2015	2016
Ambulatory (outpatient) market: Prescription + non-prescription medicines	National Health System (NHS)	NHS reimbursed		1 639	1 326	1 173	1 160	1 170	1 182	1 190
		Patients (out-of-pocket)		707	799	683	689	703	710	697
		Total NHS		**2 347**	**2 125**	**1 856**	**1 850**	**1 873**	**1 892**	**1 886**
	Non-NHS	Sub-systems	Sub-systems costs	292	166	132	69	21	20	N/A
			Patients (out-of-pocket)	114	76	58	29	5	5	N/A
			Total sub-systems	406	242	190	98	26	25	N/A
		Remaining market		513	607	600	498	540	619	N/A
	Total Ambulatory (out-patient) market)			**3 266**	**2 973**	**2 646**	**2 446**	**2 439**	**2 536**	**N/A**
NHS Hospital Market				**1 028**	**1 022**	**989**	**975**	**990**	**1 034**	**N/A**
Total Market (ambulatory + NHS hospital)				**4 294**	**3 995**	**3 635**	**3 421**	**3 429**	**3 570**	**N/A**

Sources: APIFARMA (2016) | INFARMED (2015) | INFARMED (2017a)

The total market, consisting of the sum of the ambulatory and NHS hospital market, suffered a loss of 16,9% in value from 2010 to 2015. The loss was not more pronounced due to the relative stability of the NHS hospital market expenditures with medicines (which were stable around €1.000 million.

The great majority of the NHS medicines prescriptions in 2014 were based on NHS health infrastructure, consisting of health centers and public hospitals. For instance, from a NHS expenditure point of view, the sum of these two health institution types was 74,2% (Infarmed, 2015).

The most impacting therapeutic groups in ambulatory market in terms of value in the year 2016 were oral antidiabetics (medicines taken to reduce the glucose levels in the blood, in the scope of the treatment of diabetes mellitus), modifiers of the renin angiotensin (medicines to reduce the risk of cardiovascular events and overall mortality), and anticoagulants (but evidence a substantial growth when compared against 2015) (Infarmed, 2015; Infarmed, 2017). This was mainly, as will be addressed later, due to the launch of two new oral anticoagulant drugs in the market: Pradaxa from Boehringer Ingelheim, and Xarelto from Bayer / Janssen.

Considering the main international nonproprietary names (INN) in ambulatory market, the most impacting in terms of NHS expenditures in the year 2016 were Metformine + Vildagliptine, Metformine + Sitagliptine, and Rivaroxaban (Infarmed, 2017). The first two are medicines for the treatment of diabetes mellitus type 2, and the third is an anticoagulant (drug name: Xarelto).

Considering the main commercial brands in ambulatory market, the most impacting in terms of NHS expenditures in the year 2016 were Janumet (an antidiabetic medicine from Sanofi), Eucreas (an antidiabetic medicine from Novartis) and Xarelto (an anticoagulant from Bayer), according to INFARMED (2017a). In fifth and eighth places are other anticoagulants, Pradaxa from Boehringer Ingelheim, and Eliquis from Bristol-Myers Squibb, which demonstrates the importance of this therapeutic group.

As shown in INFARMED (2017a) publication, the main marketing holders (pharmaceutical companies) in terms of NHS expenditure in the year of 2016 were Merck Sharp & Dohme (with a market share of 8,2%), Novartis Europharm (market share of 7,5%) and AstraZeneca (market share of 6,5%). The weight of the top 10 marketing authorization holders (pharmaceutical companies) on the NHS medicines expenditure reached 44,5% in 2016.

8.4.3. Medicines

The number of medicines with marketing authorization (AIM, or “Autorização de Introdução no Mercado”, in Portuguese) reached 16.428 in 2014, 10,9% more than in 2010 (Infarmed, 2015). The number of presentations (or different forms the medicines can be presented, such

as for instance packages of 10 pills, 20 pills, syrup, tube, or other), increased more than the number of brand names (7,4% vs 3,7% respectively, from 2010 to 2014). In 2014, 93% of the medicines were prescription medicines, and 39% were reimbursed by the NHS (Infarmed, 2015).

The great majority of prescription medicines are of regular prescription type. Special and restricted types include medicines subject to special and restricted medical prescription, for hospital use only (Infarmed, 2015).

8.4.4. NHS prescriptions

The number of prescriptions on the NHS reached 72,9 million in 2015, an 8,8% increase when compared to 2010 (67 million). In the same five-year period, the number of packages increased 9,4%, from 139,9 million to 153 million units (Infarmed, 2015; SNS, 2016).

In 2014, the average number of prescriptions per consultation was 1,8, the average number of packages per prescription was 2,1, and the average number of packages per consultation was 3,77 (Infarmed, 2015; SNS, 2016). The average cost per prescription borne by the NHS evidenced, from 2010 to 2015, a reduction of 44,4% (Infarmed, 2017). The average percentage of medicine NHS reimbursement was 62,5% in 2014 (Infarmed, 2017). The average cost per package has suffered substantial reductions too, especially regarding the generics, where the NHS expenditures per package decreased 68,1%, with the retail price decreasing 53,5% in the period of 2010 to 2016, as seen below in table 8.3.

Table 8.3 - NHS average cost per package in the NHS – 2010 to 2016

Units: Euros

		Scope	2010	2011	2012	2013	2014	2015	2016	% variation 2016 vs 2010
Average cost per package	Global (brands + generics)	Retail price	16,77	15,19	13,25	12,41	12,24	12,21	12,10	-27,8%
		NHS expenditure	11,72	9,48	8,38	7,78	7,65	7,63	7,63	-34,9%
		Patient charge (out-of-pocket)	5,06	5,71	4,87	4,62	4,59	4,58	4,47	-11,7%
	Brands	Retail price	17,23	16,79	16,19	15,72	15,70	15,74	15,55	-9,8%
		NHS expenditure	11,46	10,73	10,44	10,07	10,12	10,19	10,20	-11,0%
		Patient charge (out-of-pocket)	5,77	6,06	5,75	5,65	5,58	5,55	5,35	-7,3%
	Generics	Retail price	15,48	11,5	7,87	7,24	7,23	7,19	7,20	-53,5%
		NHS expenditure	12,46	6,6	4,60	4,21	4,07	4,00	3,98	-68,1%
		Patient charge (out-of-pocket)	3,02	4,9	3,27	3,03	3,16	3,19	3,22	6,6%

Source: INFARMED (2017a)

8.4.5. NHS reimbursement

The Portuguese National Health System foresaw four reimbursement categories, defined by Ordinance nr 195-D/2015, 30th of June (table 8.4).

Table 8.4 - Reimbursement categories and examples of eligible medicines

Category	Reimbursement	Examples of eligible medicines / diseases
A	90%	Hormones and medicines used to treat endocrine diseases; Medications used in ocular affections; Antineoplastic and immunomodulatory drugs
B	69%	Anti-infective drugs; Central nervous system; Cardiovascular system
C	37%	Genitourinary system; Locomotor system; Antiallergic medications
D	15%	New medicines, medicines with adjusted co-payment or medicinal products which, for specific reasons and after a reasoned opinion issued in the framework of the evaluation process of the co-payment application, are covered by a transitional co-payment scheme

The reimbursement categories vary according to: the therapeutic indications of the medicine; its use; the entities that prescribe it; and the increased consumption for patients suffering from certain pathologies.

Concerning the medications dispensed through the NHS market, the average rate of reimbursement decreased from 69,9% in 2010 to 62,5% in 2014, a loss of 7,4 percentage points (Infarmed, 2015). This loss did not seem to affect the patients, as the patients' out-of-pocket costs did not increase substantially.

8.4.6. Medicines price

The average price of medicines in the ambulatory market was €12,09 in 2015, representing a reduction of 27,9% from the average price in 2010 (€16,77). The most intense reduction occurred in 2012, with a decrease of 12,8% in the average medicines price (Infarmed, 2017). Considering generics medicines only, this reduction was significantly more pronounced, reaching 53,5% in the same period of analysis. The loss on average price is even more extreme if we compare the year 2016 against the generics average retail price in January 2007 (20,38€, according to Infarmed, 2017): 64,7% reduction. Table 8.5 provides quantitative evidence on these topics.

Table 8.5 - Average price evolution in ambulatory market – Retail value – 2010 to 2016

Units: Euro

		2010	2011	2012	2013	2014	2015	2016	2016 vs 2010
Global (brands + generics)	Average price (retail price)	16,77	15,19	13,25	12,41	12,24	12,21	12,09	---
	Variation vs previous year	---	-9,4%	-12,8%	-6,3%	-1,4%	-0,2%	-1,0%	-27,9%
Brands	Average price (retail price)	17,22	16,80	16,19	15,72	15,69	15,75	15,55	---
	Variation vs previous year	---	-2,4%	-3,6%	-2,9%	-0,2%	0,4%	-1,3%	-9,7%
Generics	Average price (retail price)	15,48	11,50	7,87	7,23	7,24	7,19	7,20	---
	Variation vs previous year	---	-25,7%	-31,6%	-8,1%	0,1%	-0,7%	0,1%	-53,5%

Source: INFARMED (2017a)

Average medicines retail price in the scope of the NHS was 12,24€ in 2014, for a correspondent NHS average expenditure of 7,65€. By dividing 7,65€ by 12,24€, one obtain the average NHS reimbursement for medicines (62,5%, as addressed before).

8.4.7. Generics

Generics medicines are faithful copies of a mature drug, no longer protected by a patent, marketed with the chemical name of the active ingredient, according to Garattini & Tediosi (2010).

The number of generic medicines with AIM increased 20,5% between 2010 and 2014, and the number of presentations increased 11,8% in the same period. The percentage of generics in the total drugs (brands and generics) gained five percentage points, from 2010 to 2014, and may have helped to contribute to the reduction of the average medicines price borne both by the NHS and by the patients (Infarmed, 2015). The generics penetration in units increased 15,9 percentage points from 2010 (31,4%) to 2016 (47,3%). A similar increase was observed in market share in DDD and in packages (with 15,1 and 15,5 percentage points increases, respectively). Considering the generified market only, generics market share reached 64,4% in 2015 and 2016, representing an increase of 11,6 percentage points from 2010.

8.5.Portuguese pharmaceutical legislative framework overview – 2000 to 2017

This sub-chapter presents a summary of the main legislative changes implemented in Portugal between the years 2000 and 2017, in the scope of the pharmaceutical market, aiming the comprehension of the Portuguese reality. Since the year 2000, the successive governments implemented several measures in order to control the medicines expenditures, including the creation of reference prices in the scope of price formation, compulsory price reductions,

development of protocols with the pharmaceutical industry to define maximum expenditures ceilings, and other measures.

8.5.1. Number of legislative initiatives

Leopold et al (2014), when comparing the effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries, presented evidence of the number of measures implemented between 2008 and 2011 in the scope of pricing, reimbursement, and generics, underlining that Portugal reached 22 measures (10 for pricing, eight for reimbursement, and four for generics), information shown in figure 8.2. A complementary analysis was performed, with a specific focus on the Portuguese legislation background. This was aimed at, by the one hand, the understanding of the complexity of the granular legislative changes that occurred in Portugal not from 1986 to 2017 (and not only from 2008 to 2011), and the quantification, by the other, of all changes including laws, decree-laws, orders, ordinances, and other legislative instruments such as protocols. For a detailed explanation of the methodology observed in this legislation search, please consult appendix 4.

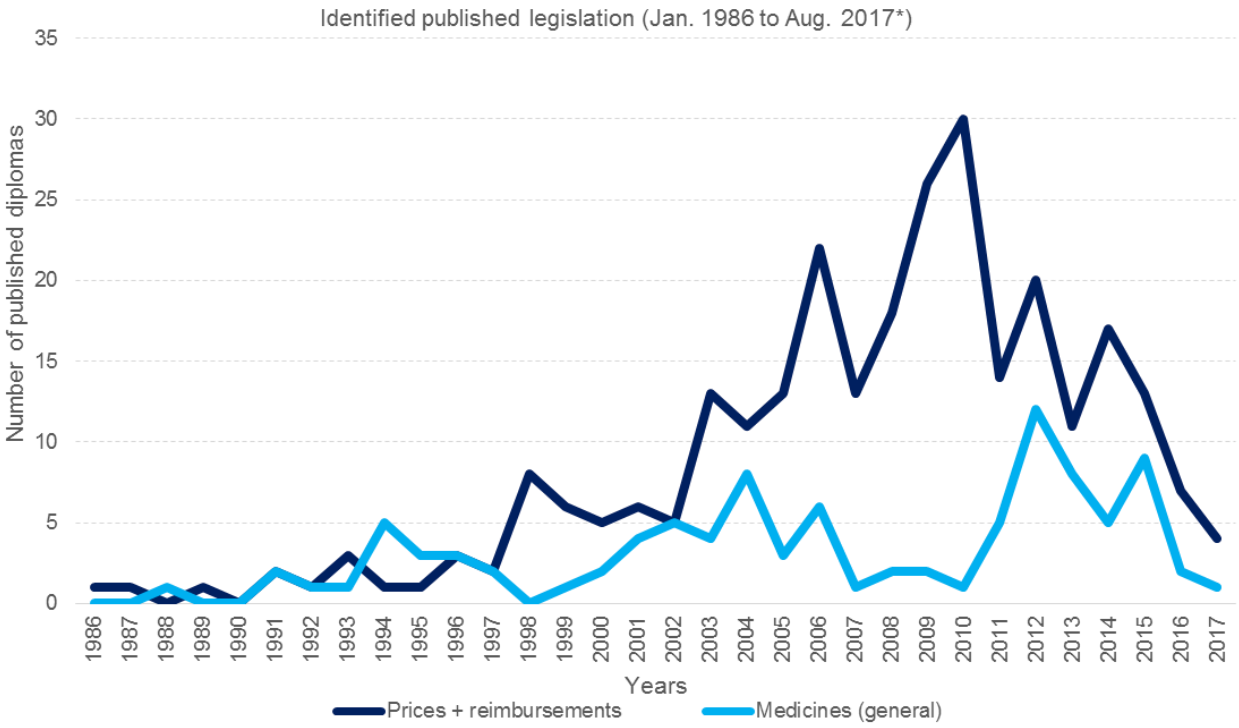


Figure 8.2 – Number of health-related legislative diplomas identified in the period of 1986 to 2017

Source: own compilation of data from INFARMED (2017b), APOGEN (2017) and PLATAFORMA (2017)

* The year of 2017 includes legislative diplomas up to August the 9th, 2017.

More than to perform a systematic and detailed inventory of the legislative changes (which was not the objective of this endeavor), the process developed aimed at targeting several goals. The first one consisted of the identification of the main legislative initiatives that could have had an impact on the market development in terms of pricing, generics penetration and market growth, for a better understanding of its dynamics. These insights were expected to help identify the therapeutic class and drug perimeter, selected for the quantitative phase of the research design, which consisted of the second objective. A third objective consisted of the critical analysis of the impact of history when interpreting the results from the quantitative and qualitative steps of the research design, especially when analyzing the internal validity.

8.5.2. Summary of the legislative initiatives

A sumary of the appendix 4 is now presented.

Prices, drug reimbursement and medicines (general) related

Taking as a reference figure 8.2, it appears that the period between the years 2006 and 2012 registered the highest numbers of legislative initiatives. Interestingly, during this period the CAGR of the NHS costs with medicines (Continental Portugal) suffered a dramatic reduction (figure 8.3).

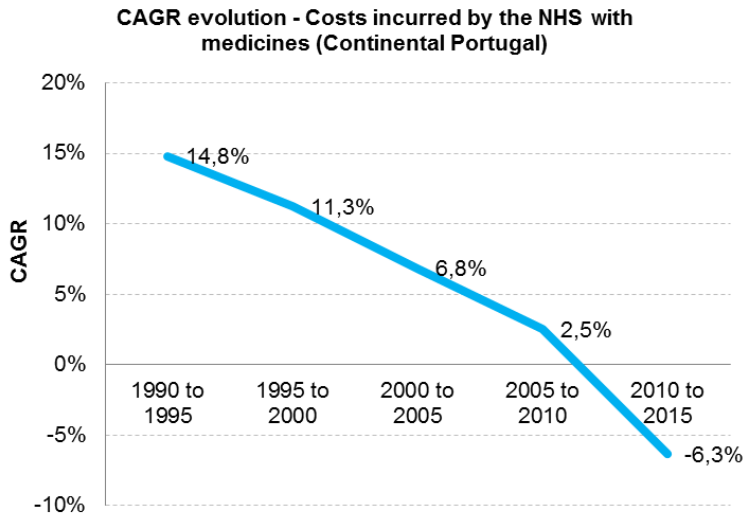


Figure 8.3 – CAGR evolution of costs incurred by the NHS with medicines (Continental Portugal)

Source: own elaboration based on available data from INFARMED (2017b)

On the compulsory side, which had a mandatory effect - in the sense that they obliged an immediate change in stakeholders' behavior, a series of measures was taken. These measures included successive changes in price formation methodology (including international reference pricing with selected countries for price comparison, and compulsory price reductions of newly launched generics medicines relative to the previous equivalent generic launched), with the goal of constraining the prices and having a better control on this variable; included mandatory price reductions in generics and non-generics prices, contributing to the control of the growth of NHS expenditures with medicines; included changes in reimbursement policy, relating reimbursement to a reference price of homogenous groups, further limiting the burden with medicines expenditures for both the NHS and to the patient. Other compulsory measures contributed also to a better control of prescriptions, better control of expenditures and behavioral changes of prescribers, and consisted of INN prescription, and electronic prescription.

Other measures were taken, not positioned as compulsory, but rather as voluntary or optional, aimed at changing attitudes and behaviors. A positive discrimination measure to promote the penetration of generic medicines was established in 2000 (taking effects during five years), consisting of a temporary 10 percentage points increase in the reimbursement of generics in reimbursement categories B, C and D. It was aimed at providing a positive incentive to prescribers and patients to choose generics. Other measures included the training given to health care professionals on the benefits of generics (503 sessions involving 7195 participants from 2001 to 2002, according to Filipe (2008), and campaigns targeted at patients, health care professionals and press, stressing the benefits of generics in terms of quality and efficacy, and later in terms of cost savings to the patient and to the society. Also in the scope of voluntary behaviors inducement, incentives were established and given to pharmacies that increased the penetration of generic medicines in their practices.

Protocols were developed with the pharmaceutical industry – through APIFARMA, which can be classified as having both a voluntary – in the sense that these protocols involved the pharmaceutical industry in the payment of part of the costs with NHS expenditures, should a certain threshold be exceeded) - and compulsory scope – in the sense that by the lack of participation could have led to a higher intensity of measures, possibly conducting to higher losses by the industry. Troika intervention led to an increase of the contribution solicited to the pharmaceutical industry, as recognized by APIFARMA (2017).

Pharmaceutical sales representatives and access to physicians

From a detailing restriction policy point of view, between 2001 and 2004, if restrictions ever existed, they must have been occasional and regional, coming from decisions of the Regional Administrations and not from the law. Between 2004 and 2006, Order 2837/2004 entered into force with restrictions that came to be declared unconstitutional with mandatory general force. As a consequence, between the declaration of unconstitutionality (December 5, 2006 or more precisely between January 4th 2007 - the date of publication of the Judgment of the Constitutional Court in Diário da República - and the Order 8213-B/2013, which entered into force in August the 1st 2013, there was a legal vacuum regarding restrictions to PSRs detailing activities. This means that regulation of marketing efforts to physicians (one of the forms of regulation noted by Stremersch & Lemmens, 2009) has taken effects from August the 1st 2013, in the form of a detailing ceiling, with the following main characteristics:

- Limit of two PSRs per day in each NHS Hospital service, or three PSRs per day in other NHS infrastructures (independently from the represented pharmaceutical companies)
- Maximum of eight visits per day to doctors working at NHS institutions (reducing two days from Order 2837/2004), per PSR. This limit may be exceeded in the case of collective information sessions, but up to a maximum of two per year for each laboratory, and covering, simultaneously, at least five health professionals
- Pharmaceutical companies can make a maximum of six visits per year to a NHS establishment or service, according to their size and the number of professionals of the different specialties that PSRs visit (in type B units integrated in the NHS - USFs, or family health units -, this number can exceptionally increase to eight visits per year, subject of notification to INFARMED

Table 8.6 below shows the summary of the main legislation related to PSRs access to NHS institutions and professionals (especially physicians).

Table 8.6 – Summary of the most relevant legislation initiatives to regulate PSRs' access to NHS institutions and professionals

Legislation	Year	Scope	Main evidence	Link to other legislation
Decree-Law 100/94, 19th April	1994	Advertising of medicinal products for human use	Articles 6 and 8 regulate the promotion to health professionals. No limit was set to the number of PSRs can make to NHS physicians	Revoked by Decree-Law 176/2006, 30th August
Order 9630/2001, 11th April	2001	Access of PSRs to the NHS system for drug promotion purposes	Regulates PSRs' right to access NHS facilities. Regional health administrations should establish standards for PSR access to the facilities of hospitals and health centers	Revoked by Order 2837/2004, 8th January
Order 2837/2004, 8th January	2004	Access to NHS establishments by PSRs	Sets limits on PSRs' access to NHS institutions and physicians (2 PSRs per day in hospital services, or 3 PSRs per day in other NHS settings; 10 visits per day maximum per PSR; 6 visits per year (maximum) per company to each NHS establishment	Revoked Order 9630/2001, 11th April
Decree-Law 176/2006, 30th August	2006	Drugs statute (the legal, manufacturing, promotion, …)	Article 157 sets the global regulation of the PSRs' activities, including training and type of information they can provide to physicians	Revokes Decree-Law 100/94, 19th April
Decision 666/2006	2006	Decision from the Constitutional Court	The Constitutional Court declares Order 2837/2004 inconstitutional, after APIFARMA asked the Public Prosecution to evaluate its constitutionality. Order 2837/2004 did not contain the express indication of the law that aimed the regulate. Therefore, Order 9630/2001 was still applicable	Inconstitutionality of Order 2837/2004
Order 8213-B/2013, 24th June	2013	Dissemination of information on medicines and health products to NHS professionals, by PSRs	Defined limits on PSRs' access to NHS institutions and NHS professionals: 2 PSRs per day in hospital services, or 3 PSRs per day in other NHS settings (health centers, USFs); 8 visits per day (maximum) per PSR; 6 visits per year (maximum) per company to each NHS establishment (or 8, observing special procedures)	Revokes Order 9630/2001

Source: own elaboration based on existing legislation

Figure 8.4 below evidences the same reality, with a visual representation of the legislation changes over time

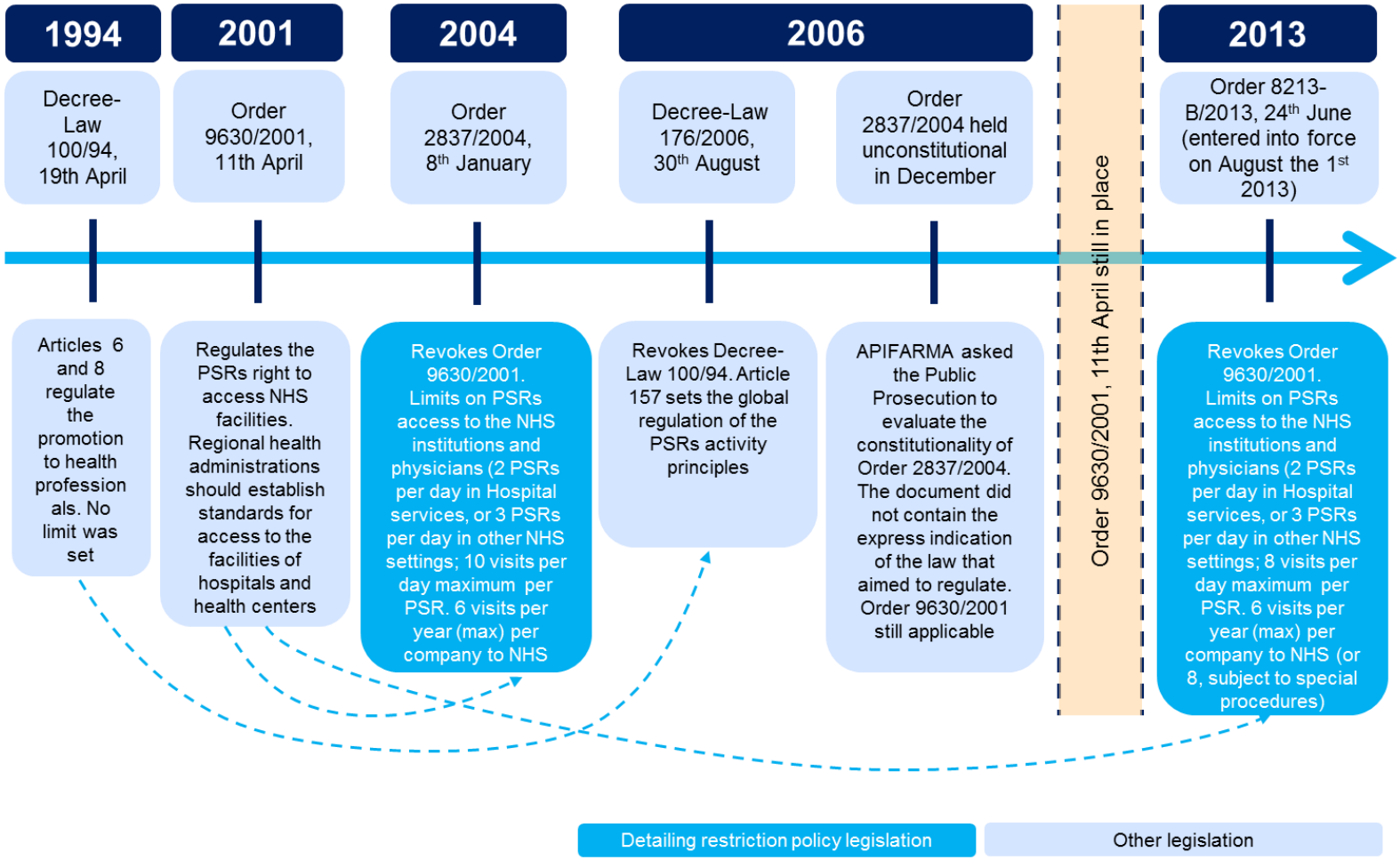


Figure 8.4 - Time frame of legislation regarding detailing restrictions in Portugal

Source: own elaboration based on existing legislation

8.6.Pharmaceutical drugs sales and promotion investments data aggregation

In the sales force effectiveness chapter, we explained that pharmaceutical companies use prescription information to qualify, segment and target physicians. This information can be disaggregated (such as in the USA, where HIOs provide pharmaceutical companies physician-level data), or aggregated in regional territories typically called bricks (Fugh-Berman, 2008).

In Portugal, Decree Law 176/2006 (30th August), which constitutes the legal regime for medicines for human use, provides, in article 158, point 5, that it is prohibited to carry out, by any means, the collection, treatment and dissemination of information regarding the prescription of medicines by persons empowered to prescribe or dispense them. This refers to physician prescription data (those empowered to prescribe), and to pharmacies dispensing data (empowered to dispense). Therefore, HIOs are not able to sell disaggregated data (physician drug prescriptions or pharmacy sales data). The only institution with legal access to physician-level prescription behavior is Serviços Partilhados do Ministério da Saúde (SPMS), an institution created in 2010 by Decree-Law 19/2010 (March 22nd).

According to SPMS (2017), its mission is to provide shared services - in the areas of purchasing and logistics, financial services, human resources and information and communication systems and technologies - to entities with specific activities in the health area, in order to "centralize, optimize and rationalize" the acquisition of goods and services in the National Health Service. SPMS develops several controls to detect fraud in prescriptions. According to the National Health System, the dematerialization of the prescriptions led to a reduction of 80% in the number of prescription-related frauds, since the year 2016 (NHS, 2017). Dispatch 7979-P/2015 determined that prescription of dispensing medicines in community pharmacy, in NHS institutions, is carried out in the PEM (Prescrição Electrónica Médica) application, and also that SPMS provides NHS institutions with data on prescription standards necessary to control and improve medical prescription and fight against fraud and waste. It also provides that doctors with private practice can request the Physicians' Chamber the PEM application.

Pharmaceutical manufacturers have control of their medicines sales to wholesalers and pharmacies. However, they miss important information. First, they do not know their sales by territory (the higher the geographic granulatity, the lower the data availability and precision); second, they do not know their competitors' sales; and third, related to the second, they do not

know their relative success versus their competitors, by territory, which does not allow companies to effectively evaluate their PSRs' teams.

As highlighted in the Portuguese Competition' Authority non-opposition decision 41/2012 (Autoridade da Concorrência, 2013), the designation "brick" in the scope of the Portuguese pharmaceutical industry refers to a classification for a particular geographical grouping of customers, that is, a grouping made through the customer's postal codes which comprises groups of three or more pharmacies and does not allow an individual identification of the transactions.

In Portugal, two HIOs provide regional drug sales, IQVIA and hMR:

- IQVIA gathers sell-in data through agreements made with the majority of the wholesalers working in Portugal (which guarantee more than 95 per cent market representativeness). As covered before, sell-in represents the wholesalers' sales to pharmacies. Sell-in data data is then compiled by brick (aggregation of at least three pharmacies) and sold to pharmaceutical manufacturers on a regular basis. IQVIA also provides sell-out data, whose data is collected from a panel of more than one thousand pharmacies, and then extrapolated to the entire universe of approximately 2.900 community pharmacies
- hmR gathers sell-out information through agreements made with the majority of the pharmacies associated with ANF (National Association of Pharmacies), which may provide better precision and reliability of data, compared to IQVIA sell-out service. Sell-out data is compiled by hmR in hmR territories, with a minimum of three pharmacies per territory

In both cases (IQVIA and hmR), each brick or territory is usually defined using postal codes, and must contain at least three pharmacies, not allowing the identification of transactions by pharmacy, in consonance with European Directive 95/46/EC on the protection of personal data. Sales by brick or territory are then used by pharmaceutical companies to define sales territories allocated to each pharmaceutical sales representative, who are therefore evaluated by the results reached in terms of the promoted drugs' market growth and market share in their allocated territory.

Two companies provide promotion investments data, IQVIA and 2Logical:

- IQVIA gathers promotion data – extracted from a IQVIA database called Channel Dynamics – which contain a series of investment tools, including detailing, e–detailing, mailing, e–mailing, meetings, events, congresses, webinars, clinical trials, journal advertising, websites, social media and samples. Promotion data is compiled by IQVIA through a representative panel of physicians that fill on–line questionnaires whenever exposed to a promotion tool (brand promoted, channel, messages, quality of the visit, and other variables). Promotion data from this panel is then extrapolated to the physician universes using a complex algorithm, regularly validated against real data. Therefore, pharmaceutical companies can have access to their relative position in terms of share of voice (given by their promotion investments divided by the global promotion investments in the eligible product market (therapeutic class)
- 2Logical provides a very similar service, based on an on-line data platform that which allows a panel of physicians to register every promotion tool impact they are impacted with (detailing, e-detailing, samples, and other promotion tools)

Differences in the availability of physician-level prescription information between countries like the USA - where information can be bought and data-mined by pharmaceutical companies - and Portugal and European Union countries - where only regional, macro-level sales data is available – implies as covered previously different prescribers segmentation and targeting approaches, and relation between companies and prescribers. The understanding of the local reality will help adapt the methodology for the empirical study.

8.7.Chapter synthesis of the main findings

This chapter started by addressing base concepts in the Portuguese health care. A distinction between primary care (the first element of the health care process, as a first point of contact of a patient with the health care system), secondary care (represents the health care services delivered by specialists, who typically do not have first contact with patients), and tertiary care (advanced or specialized medical treatment). The chapter also addressed the distinction between hospital market (where the patient does not have any participation in the decision making process of medicine choice and there is no patient financial reimbursement of the medicine cost) and ambulatory market (the patient may participate in the choice and may have to pay for part of the medicine retail selling price, outside a hospital setting). It distinguished

between inpatients (admitted at a health care infrastructure and staying there for more than 24 hours, occupying a bed) and outpatients (with health issues which do not require hospitalization).

The chapter then addressed brief bases of health economics in Portugal. The country suffered two negative impacts in the last decade (the international crisis in 2009, generating a decline of 3% in the GDP that year, and the budget austerity measures imposed by the Troika in 2011, with a profund negative impact on GDP growth rates (negative for the three years after the intervention). The country has evidenced a relatively stable proportion of the GDP allocated to health expenditures (between 8,9% and 9,9%, but the lower GDP in absolute value left to a lower investment in health expenditures. The Portuguese NHS medicines market evidenced a substantial negative growth from 2010 to 2015 (-16,9%). This reduction had impact on NHS costs with medicines, given that out-of-pocket costs remained relatively stable. The cost savings obtained by the NHS resulted in a reduction of 44,4% in the average cost per prescription (from 2010 to 2015), which allowed the NHS to reduce the average reimbursement rate. The average price of medicines in the ambulatory market dropped from €16,77 in 2010 to €12,09 in 2015 (-27,9%). The generics penetration increased from 31,4% in 2010 to 47,3% in 2016 in units, and from 52,8% in 2010 to 64,4% in 2015 in the generified market.

The chapter also analyzed the Portuguese pharmaceutical legislative framework, with a special focus on the period of the years 2000 to 2017. The substantial growth of medicines related expenditures observed during the first decade of the 21st century, allied to the fact that a substantial proportion of the global health care costs are fixed (personnel, infrastructures), and given the marginal penetration of generics, may have contributed to the implementation, by successive governments, of a series of measures aimed at reducing the NHS and patients cost burden with medicines, whose effects were compulsory in some cases, while voluntary of optional in other cases. The period between the years 2006 and 2012 registered the highest numbers of legislative initiatives in the scope of price, reimbursement, and medicines in general, and included several measures to contrain the NHS expenditures with medicines such as changes in price formation methodology (international reference pricing and compulsory price reductions), changes in reimbursement policy (reference price of homogenous groups), INN prescription, and electronic prescription. Positive discrimination was implemented to help the penetration of generics, with temporary surcharge of the reimbursment. Protocols were developed with the pharmaceutical industry, involving the payment of part of the costs

with NHS expenditures, should a certain threshold was exceeded. Specific legislation was implemented, in 2013, to regulate PSRs' access to NHS doctors and institutions. This included detailing ceilings, below briefly characterized:

- Limit of two PSRs per day in each NHS Hospital service, or three PSRs per day in other NHS infrastructures (independently from the represented pharmaceutical companies)
- Maximum of eight visits per day to doctors working at NHS institutions, per PSR (exceptions may apply, in the scope of collective information sessions)
- Pharmaceutical companies can make a maximum of six visits per year to a NHS establishment or service, according to their size and the number of professionals of the different specialties that PSRs visit (exception may apply, in the case of type B health family units

Finally, the chapter approached the particular reality of the Portuguese pharmaceutical market in terms of access to drug sales and promotion tools data. It explained that the provision of disaggregated (individual-level) sales data is not legally allowed, and that HIOs provide pharmaceutical companies regional-level data, providing sales data per IQVIA brick or by hmR territory. Promotion tools investments data is provided by HIOs at a national level, without any regional aggregation.

The characterization of the Portuguese situation – with all its specificities – will allow the adaptation of the methodology to be applied in the empirical study of this thesis.

9. Methodology

This chapter describes the methodology observed throughout the development of this thesis, from literature review to data analysis procedures.

9.1.Literature review

The starting to conduct the literature review was the selection of the eligible key words. Given the scope of the thesis, several keywords were selected, which were the following:

- Pharmaceutical marketing
- Pharmaceutical promotion
- Detailing and prescription
- Pharmaceutical regulation
- Detailing restriction policies

The second decision was to select the scientific search engines for the articles. The options chosen were EBSCO-host (Business Source Complete) and b-on (on-line knowledge library, which gathers several international scientific libraries), and the search process started on October 2016.

In a first moment, 123 articles were selected and abstracts were extracted and compiled into a single database in word processor format (DOC), with a balanced selection of less recent and more recent articles. The reading of these abstracts allowed a first understanding of the main concepts addressed by previous researchers in the pharmaceutical marketing and regulation and policy fields, and the most used methods for data analysis (quantitative using time series, quantitative using cross-sectional research, and qualitative using in-depth interviews and focus groups). A special attention was given to the future research suggestions given by the scholars. As the literature review was developed, other references were extracted, adding articles from journals with high impact factors; articles with a substantial amount of citations; and articles often referenced by the most active researchers in this field. A special attention was given to the time horizon of the publication date, including as far as possible articles from 1980 to 2019, allowing the study of not only the historical references in this field, but also of more contemporaneous research. This process resulted in a final perimeter of 289 peer-reviewed articles analyzed. In the literature review process, we also analyzed a selection of 146 non-peer reviewed sources including pharmaceutical industry associations' reports, pharmaceutical companies' websites and reports, consulting companies' reports, national health system legislation and reports, white papers from experts, reference books, and other,

many of which cited in peer-reviewed articles (for instance, IQVIA syndicated data regarding medicines sales, promotion investment magnitude, and other).

9.2.Empirical study

In this sub-chapter, the methodology observed to develop the empirical study is explained.

9.2.1. Research method approach

The empirical study observed a mixed research method, using a sequential explanatory design. The selection of this research approach was based on four main reasons. First, the search for comprehensiveness, as highlighted by O'Cathain, Murphy & Nicholl (2007), engaging with the «*complexity of health, health care interventions, and the environment in which studies took place*» (p. 85). Second, to obtain a better understanding of the research problem «*by converging broad numeric trends from quantitative research, and the detail of qualitative research*», as underlined by Creswell (2009, p. 121). Third, to allow a more detailed understanding of the data by «*using qualitative follow–up data to help explain a quantitative database*», as pointed by Creswell (2014, p. 177). Fourth, the fact that qualitative research can facilitate the interpretation of the relationship between the variables selected for analysis, as suggested by Bryman & Bell (2015). These last authors also underline the fact that «*quantitative and the qualitative data deriving from mixed research methods research should be mutually illuminating*» (p. 641), and that «*triangulation involves using more than one method or source of data in the study of social phenomena*» (p. 402).

In terms of sequence, the research observed the following steps, here shown in figure 9.1:

Figure 9.1 - Research method approach

Source: adapted from Creswell (2009)

9.2.2. Epistemological and Ontological perspectives

The research method can be positioned in terms of role of theory in relation to research, epistemological and ontological orientation, and other characteristics, summarized below in table 9.1. Using an adaptation of Bryman & Bell (2015) framework, the role of theory of the quantitative phase will be deductive, allowing the testing of theory, whereas the qualitative phase will be inductive, aimed at the possible generation of theory. In terms of epistemological orientation, the quantitative phase will use a natural science model (positivism), while the qualitative phase will use an interpretivist model. In what regards the ontological orientation, the quantitative phase (objective, and allowing generalization) will follow an objectivism approach, whereas the qualitative phase (subjective, aimed at studying the uniqueness) will observe a constructivist approach.

Table 9.1 – Epistemological and ontological perspectives of the research model approach

	Quantitative – 1st phase	Qualitative – 2nd phase
Role of theory in relation to research	Deductive | Testing of theory	Inductive | Generation of theory
Epistemological orientation	Natural science model, in particular positivism	Interpretivism
Ontological orientation	Objectivism	Constructivism
Other characteristics	Objective Generalization	Subjective Uniqueness

Source: adapted from Bryman & Bell (2015)

9.2.3. Quantitative phase

The research design that was observed to answer the research question comprised five dimensions: objective of the research, control used in the research, context of the research, time in terms of data availability, and data collection. Table 9.2 below summarizes the research design applied in the quantitative phase of the empirical study:

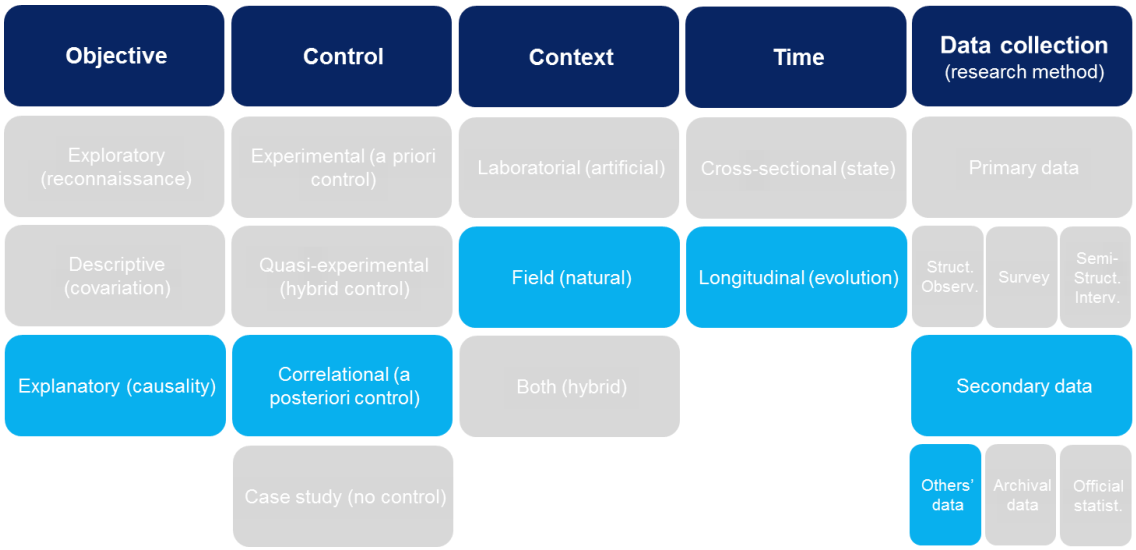


Table 9.2 - Research design scheme for the quantitative phase

9.2.3.1.Research objective, control and context

In terms of the research objective, the proposed research was explanatory in the first phase, studying the causal effect of the detailing activities on the prescription behavior through time, before and after the entry into force of a compulsory detailing ceiling.

From a control point of view, the proposed research was correlational in the first phase (quantitative), using a posteriori control, since the database that was used in this phase had already been created.

In terms of context, the quantitative phase is classified as field (natural). The research was conducted in the natural habitat, in the real world, and not confined to an artificial or laboratory setting.

The selection of this research design (objective, control and context) for the quantitative phase was aligned with the designs used by the majority of the researchers in the pharmaceutical marketing community. These include (but not limited to) Gönül, Carter, Petrova & Srinivasan (2001), Narayanan, Manchanda & Chintagunta (2003), Mizik & Jacobson (2004), Manchanda & Chintagunta (2004), Manchanda & Chintagunta (2005), Manchanda & Honka (2005), Kalyanaram (2009), Fischer & Albers (2010), Montoya, Netzer & Jedidi (2010), Riese et al (2015), Datta & Dave (2016), and Liu et al (2016).

9.2.3.2.Time

Concerning time, the research was longitudinal in the quantitative phase, as observed by researchers in the pharmaceutical marketing community for quantitative research. A time series of sales and marketing investments data was used. Some of the authors using time series data include (but not limited to) Narayanan, Manchanda & Chintagunta (2003), Mizik & Jacobson (2004), Fischer & Albers (2010), and Liu et al (2016). In order to analyze the impact of detailing on prescription behavior before and after the entry into force of the compulsory detailing ceiling in NHS infrastructure, a data series of six years was used (three years before the detailing ceiling, and three years after it went into force).

9.2.3.3.Data collection

Portugal is a very specific, highly restricted market, with absence of official published monthly data about individual medicines sales and promotion activities. By the one hand, prescription data is available to Infarmed only, but not available publicly. By the other hand, promotion data is only partially publicly available through Placotrans (Infarmed), but it is not organized and compiled properly, and misses the detailing activities (pharmaceutical manufacturers are not obliged to disclose detailing activities in Placotrans).

Regarding data collection and research method, the quantitative phase used secondary data, collected by IQVIA, an American Health Information Organization and consulting company that resulted from the merger between IMS Health and Quintiles, and which provides services to the pharmaceutical industry. IQVIA (or companies acquired by former IMS Health, such as Verispan / Scott Levin, and SDI Health) has been the main data provider for research in the pharmaceutical marketing community, providing data for authors that studied detailing, including (but not limited to) Berndt et al (1995), Auvray, Hensgen & Sermet (2003), Rosenthal, Berndt, Donohue, Epstein & Frank (2003), Narayanan, Desiraju & Chintagunta (2004), Chintagunta & Desiraju (2005), Manchanda et al (2005), Windmeijer, de Laat, Douven & Mot (2006), Berndt, Danzon & Kruse (2007), Kalyanaram (2008), Kremer, Bijmolt, Leeflang & Wieringa (2008), Manchanda, Xie & Youn (2008), Vakratsas & Kolsarici (2008), Dong, Manchanda & Chintagunta (2009), Kalyanaram (2009), Ching & Ishihara (2012), Fischer & Albers (2010), Gönül & Carter (2010), Dong, Chintagunta & Manchanda (2011), Dave & Saffer (2012), Datta & Dave (2016), and Kappe & Stremersch (2016).

The time series data IQVIA provided consisted, by the one hand, of sales of eligible medicines through time, called sell–in data, defined as sales valued at the wholesale price (or

price pharmacies pay to the wholesalers in the pharmaceutical marketing channels), and by the other hand of promotion investments made by pharmaceutical companies (including detailing).

Sales data was gathered by IQVIA through agreements made with the majority of the wholesalers working in Portugal (>95% market representativeness, and therefore we consider it as populational data). Promotion data – extracted from an IQVIA database called Channel Dynamics – contains a series of investment tools, including detailing. Promotion data was compiled by IQVIA through a representative panel of physicians that fill on–line questionnaires whenever exposed to a promotion tool (identifying the brand promoted, the promotion tool used, writing the messages, qualifying the quality of the visit, and other variables). Promotion data from this panel was extrapolated to the physician universes using a complex algorithm, regularly validated against real data. We consider, for the purpose of this thesis, that promotion data is representative, allowing us to infer results from the sample to the whole population of doctors.

9.2.3.4.Markets classes selection

The markets included in the data extraction were defined using a three-fold procedure.

First, we identified and quantified the most studied markets and therapeutic classes in the previous research perimeter presented before. For this, we built table 9.3, where in column we present the therapeutic areas analyzed in each of the articles.

Table 9.3 – Most studied therapeutic areas in the scope of detailing

Author(s)	Anonymous / vague	Tranquilizers / anti-depressants	Anti-hyperlipidemic (cholesterol)	Anti-ulcers	Anti-histamines (allergies)	Anti-hypertension	Respiratory (asthma / COPD)	Anti-rheumatic / arthritis	Erectile dysfunction	Other	Anti-epileptics	Anti-migraine	Anti-virals	Diuretics	Oral contraception
Parsons & Abeele (1981)	√														
Mackowiak & Gagnon (1985)		√												√	
Berndt, Bui, Reiley & Urban (1996)				√											
Rizzo (1999)						√									
Gönül, Carter, Petrova & Srinivasan (2001)	√														
Wittink (2002)						√	√	√	√	√					
Wosinska (2002)			√												
Narayanan, Manchanda & Chintagunta (2003)					√										
Rosenthal, Berndt, Donohue, Epstein & Frank (2003)		√	√	√	√										
Manchanda & Chintagunta (2004)	√														
Manchanda, Rossi & Chintagunta (2004)	√														
Mizik & Jacobson (2004)	√														
Narayanan, Desiraju & Chintagunta (2004)					√										
Chintagunta & Desiraju (2005)		√													
Narayanan, Manchanda & Chintagunta (2005)					√										

Author(s)	Anonymous / vague	Tranquilizers / anti-depressants	Anti-hyperlipidemic (cholesterol)	Anti-ulcers	Anti-histamines (allergies)	Anti-hypertension	Respiratory (asthma / COPD)	Anti-rheumatic / arthritis	Erectile dysfunction	Other	Anti-epileptics	Anti-migraine	Anti-virals	Diuretics	Oral contraception
Windmeijer, de Laat, Douven & Mot (2006)		√	√	√	√	√	√	√				√			√
Berndt, Danzon & Kruse (2007)		√				√					√				
Venkataraman & Stremersch (2007)			√						√	√					
Kalyanaram (2008)		√		√	√										
Manchanda, Xie & Youn (2008)	√														
Vakratsas & Kolsarici (2008)	√														
John (2008)	√														
Dong, Manchanda & Chintagunta (2009)				√											
Kalyanaram (2009)		√		√	√										
Narayanan & Manchanda (2009)									√						
Fischer & Albers (2010)	√														
Fischer, Leeflang & Verhoef (2010)						√									
Gönül & Carter (2010)	√														
Leeflang & Wieringa (2010)	√														
Montoya, Netzer & Jedidi (2010)	√														

Author(s)	Anonymous / vague	Tranquilizers / anti-depressants	Anti-hyperlipidemic (cholesterol)	Anti-ulcers	Anti-histamines (allergies)	Anti-hypertension	Respiratory (asthma / COPD)	Anti-rheumatic / arthritis	Erectile dysfunction	Other	Anti-epileptics	Anti-migraine	Anti-virals	Diuretics	Oral contraception
Nair, Manchanda & Bhatia (2010)	√														
Dong, Chintagunta & Manchanda (2011)		√		√											
Ching & Ishihara (2012)						√									
Dave & Saffer (2012)		√	√	√						√					
Wieringa & Leeflang (2013)		√	√	√		√	√								
Ruiz-Conde, Wieringa & Leeflang (2014)					√		√	√							
Datta & Dave (2016)													√		
Kappe & Stremersch (2016)			√												
Liu, Gupta, Venkataraman & Liu (2016)			√												
Mukherji, Jaimakiraman, Dutta & Rajiv (2016)			√												
Chung, Kim & Park (2017)	√														
Kappe, Venkataraman & Stremersch (2017)			√												
Liu, Liu & Chintagunta (2017)													√		
Shapiro (2018)										√					

Source: own elaboration

The above presented table can be further summarized, in order to allow the quantification of the most studied markets. By counting the number of areas, in each column, we obtained the following results, shown below in table 9.4:

Table 9.4 – Markets counts on previous research

	Nr of articles
Anonymous / vague	13
Tranquilizers / anti-depressants	10
Anti-hyperlipidemic (cholesterol)	9
Anti-ulcers	9
Anti-histamines (allergies)	8
Anti-hypertension	7
Respiratory (asthma / COPD)	4
Anti-rheumatic / arthritis	3
Erectile dysfunction	3
Other	3
Anti-epileptics	1
Anti-migraine	1
Anti-virals	1
Diuretics	1
Oral contraception	1

Source: own elaboration

Considering the article perimeter selected for analysis, the most studied therapeutic areas are tranquilizers / anti-depressants, anti-hyperlipidemics, anti-ulcers, anti-hystamines, and anti-hypertension. Comparing these five areas against IMS Institute (2016) report on medicines use and spending in the US, we find that, except for anti-histamines, all the other areas are present in the top 20 therapeutic classes by spending in the USA, in the year 2015.

We also looked at Kremer et al (2008) 252 detailing elasticities addressed in their review, here summarized in 9.5.

Table 9.5 – Kremer et al (2008) number of elasticities by disease category

	Nr of elasticities
Inflammations	16
Heart and vascular diseases	33
Hypersensitivity	35
Skin diseases	40
Neurology and psychology	42
Other	86
	252

Source: Adapted from Kremer et al (2008)

Despite the different disease categorization, tables 9.4 and 9.5 suggest a reasonable alignment on the main therapeutic or disease areas previously studied in the scope of detailing. For instance, we can include anti-hyperlipidemic (cholesterol) and anti-hypertension in Kremer et al (2008) heart and vascular diseases group, or anti-histamines (allergies) and respiratory (asthma / COPD) in Kremer et al (2008) hypersensitivity group, or tranquilizers / anti-depressants, anti-epileptics and anti-migraine in Kremer et al (2008) neurology and psychology group. The only group that is not represented in the articles we selected as perimeter is Kremer et al (2008) group skin diseases.

Second, since the empirical study was targeting therapeutic classes in the Portuguese market, it was important to guarantee that the selected markets had an adequate representativeness in terms of health expenditure. Therefore, we analyzed the top 10 most important classes in Portugal, in 2016, according to INFARMED (2017a). The results are shown below, in table 9.6.

Table 9.6 – 2016 NHS expenditures with medicines, by pharmachoterapeutic classification

Rank	Pharmacotherapeutic Classification	Main pathologies	Weight in NHS expenditures
1	Other anti-diabetics	Diabetes	15,3%
2	Renin-angiotensin axis modifiers	Hypertension	8,4%
3	Anticoagulants	Blood clot prevention	7,8%
4	Antipsychotics	Psychiatric disorders	5,8%
5	Insulines	Diabetes	5,6%
6	Antidyslipidemic	Cholesterol	5,1%
7	Other antiasthmatics and bronchodilators	Asthma / COPD	4,2%
8	Antiepileptics and anticonvulsants	Epilepsy	3,8%
9	Antidepression	Depression	2,7%
10	Other antihypertensives	Hypertension	2,6%

Source: adapted from INFARMED (2016)

Third, the insights gathered during a series of non–structured interviews with pharmaceutical industry specialists, which took place from April 2017 to January 2018, allowed the generation of additional insights. Based on the previous two steps, we compiled a list of 12 classes, which were presented to specialists in pharmaceutical markets and therapeutic classes in Portugal. These 12 markets were the ones shown below in table 9.7.

Table 9.7 – Markets selected for discussion with specialists

List of 12 markets presented to the specialists
Anti-depressants
Anti-epileptics and anti-convulsants
Anti-histamines (allergies)
Anti-hyperlipidemic (cholesterol)
Anti-hypertension
Anti-psychotics
Anti-ulcers
Erectile dysfunction
Oral anticoagulants
Oral antidiabetics
Oral contraception
Respiratoru (asthma / COPD)

Source: own elaboration

The two last non-structured interviews, which occurred between the 24th and the 26th of January 2018, were particularly insightful. These two specialists – both working at IQVIA, the company resulting from the merger between IMS Health and Quintiles – were asked to indicate, from the classes above, the ones with the most potential and interest to be studied, given:

- Their importance in the Portuguese pharmaceutical market (in terms of market value and pathology prevalence)

- The occurrence, in the last eight to 10 years, of generification (loss of patent of investigation brands, and entry of generics)

- The occurrence, in the last eight to 10 years, of new entries of investigation drugs

- The impact of generics in the class - the Portuguese pharmaceutical market has been subject to substantial new regulations in the last decade, so it was important to highlight that a selection criteria would be to consider at leasttwo classes more exposed to generics, and at least two less exposed

One of the specialists – project manager, age range >55, with 35+ years of professional experience, the last 13 of which in the pharmaceutical industry, in the classification of products in their correspondent therapeutic classes - indicated five classes, and another – account manager and solutions lead, age range 30-35, with ten years of experience in the Portuguese pharmaceutical market, therapeutic class dynamics and evolution through the years - indicated six classes. Of these, five are an exact match from the ones proposed by the first specialist. Both specialists were asked whether there were other classes – other than the 12 shown – with interest in terms of analysis. No other classes were spontaneously suggested.

The data provider of the time series requested that the classes should remain confidential, as well as the products in each class. Given this restriction, we present only the main area the class deals with. The classes selected for analysis are, therefore, the following (table 9.8):

Table 9.8 – Perimeter of markets selected for analysis in the empirical study

Market	Present in top 6 in expenditure in PT (Infarmed)?	Market studied by previous researchers?	Relevance confirmed by industry expert 1?	Relevance confirmed by industry expert 2?	Exposure to generics	%NHS expenditure with medicines on selected markets (2016)	Number of products modelled	Weight of the selected products on its defined market (€) (2012-2015)
Market 1 - Blood -	Yes	Yes	Yes	Yes	Low	>35%	3	100%
Market 2 - Pancreas -	Yes	No	Yes	Yes	Low		5	67%
Market 3 - Heart -	Yes	Yes	Yes	Yes	Moderate		5	43%
Market 4 - Liver -	Yes	Yes	Yes	Yes	High		5	55%

Source: own elaboration

The goal of this process was to obtain a list of markets which can contribute to both the theory, building on previous research, but also to the pharmaceutical practice, by selecting relevant, representative and current classes that make sense in the Portuguese market. The combined weight of these four markets accounted for more than three thirds of the NHS expenditures with medicines.

As evidenced previously, all of the selected markets are important in terms of ATC global sales in Portugal. As explained by Olson & Singh (2017), the Anatomical Therapeutic Chemical (ATC) codes were created by the World Health Organization (WHO), assigning a code to drugs, based on their therapeutic and pharmacological characteristics. They explicated that «*the ATC system has a tree-based hierarchy with five levels, each describing a new level of detail of a drug's therapeutic profile as described in the following: first level: One letter signifying which of the 14 anatomical groups the drug acts on. Second level: two digits that represent the therapeutic group of the drug. Third and Fourth levels: one letter each specifying therapeutic and pharmacological subgroups. Fifth level: two digits that are used to identify the drug within its group*» (p. 20). They presented an example regarding aspirin, shown below in figure 9.4.

ATC Level	ATC Codes of Aspirin	
	Antiplatelet effects	*Anti-fever/pain reliever*
1: Anatomical main group	***B*** : Blood and Blood forming agents	***N*** : Nervous System
2: Threaputic main group	**B*01*** : Antithrombotic Agents	**N*02***: Analgesic
3: Therapeutic/pharmacological subgroup	**B01*A*** : Antithrombotic Agents	**N02*B***: Other analgesics and Antipyretics (fever reducers)
4: Chemical/therapeutic/pharmacological subgroup	**B01AC** : Platelet aggregation inhibitors excl. heparin	**N02BA**: Salicylic acid and derivatives
5: Chemical substance identifiers	**B01AC*06*** : Acetylsalicylic acid	**N02BA*01***: Acetylsalicylic acid

Figure 9.2 – ATC Codes for aspirin (in bold)

Source: Olson & Singh (2017)

9.2.3.5.Brands' selection in each market

After the definition of the markets, the next step consisted of the selection of the products to analyze, with a goal of five products per market. We observed the following general criteria for this selection, for each market (period of analysis from January 2012 to December 2015):

- We started by selecting the three products with the highest sell-in sales in Euros;
- Then we selected one brand that has entered the market during the period of analysis. When more than two brands existed in this situation, the one starting its sales closer to January 2012 was selected, in order to maximize the time series available for analysis;
- Thereafter, we selected one brand that has lost patent protection during the period of analysis; When more than two brands existed in this situation, we selected the one that started facing competition from generics closer to January 2012, in order to maximize the length of the time series available for analysis;

- In the situations where there were no new brands that started suffering from generics competition during the period of analysis, we selected another brand of interest (one promoted in co-marketing with one of the top three brands). There were other situations of co-marketing too, among products already in the top 3 of sell-in sales in Euros.

With these criteria, we aimed to maximize the validity and generalization ability of the research performed, including not only the top three brands, but also new brands entering the market, mature brands losing their patent protection, and brands promoted in co-marketing with one or more of the top three brands in terms of sell-in sales. The effect of the detailing ceiling on a multitude of situations was then be possible (in some cases though the loss of patent protection or the start of commercialization were initiated after the entry into force of the detailing celing).

9.2.3.6.Competitors' selection for each brand

Since one of the independent variables in our model is competitive promotion investments (especially competitive detailing), we then identified the main competitors of each brand in each market. This was performed in two ways:

- First, we analyzed the drug sales ranking in each market and identified a first group of possible competitors for each brand
- Second, we analyzed the indications of each brand using INFARMED's INFOMED website, where we consulted the patient information leaflet, to understand whether the competitors were targeted at addressing the same pathologies. The weblink used for this selection was http://app7.infarmed.pt/infomed/
- Third, in order to validate the provisional list of the main competitors for each brand, we interviewed specialists working in the pharmaceutical industry, with direct experience in studying and managing brands in the selected markets. These interviews occurred between the 11th and 18th of April 2018. The profile of the interviewed managers was the following:
    - Interviewed 1 - >50 years old, >10 years of experience in market research, in a company present in the top 3 in sell-in sales in one of the markets
    - Interviewed 2 – 35-40 years old, ≥10 years of experience in consultancy and market research projects managing products in all the selected markets

The final list of competitors for each of the brands in each market was then completed. We selected up to five main competitors for each product.

9.2.3.7.Data analysis model

In terms of data analysis model, one could expect to use the model applied by Liu et al (2016). However, since we used aggregated data instead of disaggregated data, and given that we did not need to develop counterfactual simulations because we had access to real market data before and after the implementation of a detailing ceiling, we performed a specific search for a suitable data analysis model, focusing on previous research related to the detailing impact on prescription behavior. The research perimeter was set by analyzing – from all the global peer-reviewed references cited in this thesis – the articles exploring time-series data regarding detailing.

Table 9.9 highlights the main findings gathered. This table characterizes each article in terms of data aggregation (nominatively at physician leel, or market level), level of analysis (brand or drug category), the quantitative model used, the dependent and independent variables used, and additional information about the model in terms of the use of non-linear detailing terms, detailing lagged terms, detailing stock (carryover), detailing stock discount (or wearout, or decay), and detailing monthly discount rate (whenever applicable).

Table 9.9 – Data aggregation, level of analysis, and quantitative model used by previous researchers

	Data aggregation		Level of analysis				Independent variables		Includes detailing...				
Author(s)	**Physician**	**Market**	**Brand**	**Category**	**Model**	**Dependent variable**	**Promotion tools**	**Other**	**Non-linear term?** (quadratic, log, or other)	**Lagged terms?**	**Stock / carryover?**	**Stock discount** (decay / wearout?*	**Monthly discount rate**
Parsons & Abeele (1981)		√	√		OLS regression model	Sales (prescriptions)	Detailing; mailing; samples; handouts	Gender	No	No	No	---	---
Mackowiak & Gagnon (1985)		√	√		ARIMA Time series analysis	Sales (new prescriptions)	Detailing; journal advertising	---	No	Yes	No	---	---
Berndt, Bui, Reiley & Urban (1996)		√	√		NL-2SLS (non-linear two stage least squares) regression model	Market share	Detailing; medical journal advertising; DTCA	Price; longevity in the market	No	No	Yes	Yes	4.2%
Rizzo (1999)		√		√	Multivariate regression model	Sales (prescriptions)	Detailing; competitors detailing	Drug price; competitors price; drug age; other factors	Yes	No	Yes	Yes	Consumer price index
Gönül, Carter, Petrova & Srinivasan (2001)	√			√	Multinomial logit model with na unknown number of latent classes and interactions	Sales (prescriptions)	Detailing; samples	Retail price; insurance	Yes	No	Yes	Yes	0.1%
Wittink (2002)		√	√		Ordinary Least Squares (OLS) Regression	Sales (prescriptions)	Detailing; DTCA; Journal advertising; Physician meetings	Retail price	No	No	No	---	---
Wosinska (2002)		√		√	Mixed logit model	Sales (new prescriptions)	Detailing; samples; DTCA	Off formulary; other variables	Yes	Yes	Yes	Yes	0.3%
Narayanan, Manchanda & Chintagunta (2003)		√	√		Structural model of demand; random coefficients discrete choice model; Bayesian learning process; GMM-based methodology	Sales (new prescriptions)	Detailing; DTCA; meetings & events	Past experience; retail price	No	Yes	Yes	Yes	30.0%
Rosenthal, Berndt, Donohue, Epstein & Frank (2003)		√	√	√	Cobb-Douglas demand specification (log-log)	Sales (prescriptions)	Detailing; samples; DTCA	Drug price; order of entry; drug age (time remaining with patent)	No	No	No	---	---
Manchanda & Chintagunta (2004)	√		√		Hierarchical Bayesian count data model and Markov chain Monte Carlo methods; Poisson regression (physician prescriptions)	Sales (prescriptions)	Detailing; samples	Specialty; gender	Yes	No	No	No	---
Manchanda, Rossi & Chintagunta (2004)	√		√		Negative binomial distribution (NBD) regression (sales response function); Poisson distribution for detailing, joint hierarchical Bayes procedure	Sales (prescriptions)	Detailing; samples	Specialty	No	Yes	No	No	---
Mizik & Jacobson (2004)	√		√		Dynamic fixed-effects distributed lag regression model	Sales (new prescriptions)	Detailing; samples	Specialty; Competitors prescriptions	No	Yes	No	---	---

	Data aggregation		Level of analysis				Independent variables		Includes detailing…				
Author(s)	**Physician**	**Market**	**Brand**	**Category**	**Model**	**Dependent variable**	**Promotion tools**	**Other**	**Non-linear term?** (quadratic, log, or other)	**Lagged terms?**	**Stock / carryover?**	**Stock discount** (decay / wearout?*	**Monthly discount rate**
Narayanan, Desiraju & Chintagunta (2004)		√	√		Linear sales model for category sales and a discrete choice model for brand share; standard Nerlove–Arrow (1962) exponential decay goodwill model (log-linear)	Sales (prescriptions)	Detailing; DTCA; meetings & events; interactions	Retail price; seasonality	No	Yes	Yes	Yes	14.0%
Chintagunta & Desiraju (2005)		√	√		Mixed logit model | Generalized method of moments (GMM) (log-log)	Market share	Detailing; other marketing investments (samples, journal advertising); competitors detailing	Drug price; avg competitors price; seasonality	No*	Yes	Yes	No	---
Narayanan, Manchanda & Chintagunta (2005)		√	√		Structural model of demand; random coefficients discrete choice model with a Bayesian learning process	Sales (new prescriptions)	Detailing; DTCA; meetings & events	Retail price; time	No	Yes	Yes	Yes	30.0%
Windmeijer, de Laat, Douven & Mot (2006)		√		√	Modified Rizzo OLS regression model	Sales (Defined Daily Doses)	Drug promotion (detailing + advertising + direct mail); interactions; competitors promotion expenditures	Drug price; avg competitors' drug price, drug age; others	No	No	Yes	Yes	4.6%
Berndt, Danzon & Kruse (2007)		√		√	Multivariate regression models	Sales (prescriptions)	Detailing	Demographic and economic measures	No	Yes	Yes	No	---
Venkataraman & Stremersch (2007)	√		√		Econometric model (negative binomial distribution (NBD) model)	Sales (prescriptions); samples dispensed	Detailing; meetings	Patient requests; drug characteristics	No	No	No	---	---
Kalyanaram (2008)		√	√		OLS regression model	Market share	Detailing + journal advertising (DTPP); DTCA	Retail price; order of market entry	No	No	No	---	---
Manchanda, Xie & Youn (2008)	√		√		Binary choice model with duration dependence (equivalent to a discrete-time-hazard (survival) model (Wheat and Morrison 1990))	Sales (prescriptions)	Detailing; samples; DTCA	Time; contagion variables	No	No	Yes	Yes	30.0%
Vakratsas & Kolsarici (2008)		√		√	Switching regime dual-market diffusion model (extension of the Generalized Bass Model (GBM))	Sales (new prescriptions)	Detailing; journal advertising; DTCA	---	No*	Yes	No	---	---
John (2008)	√		√		Neural networks and non-linear programming	Sales (prescriptions)	Detailing	---	Yes	No	Yes	No	---
Dong, Manchanda & Chintagunta (2009)	√		√		Bayesian method with a prescription response model and a strategic detailing equation | Poisson-lognormal distribution	Sales (prescriptions)	Detailing	---	Yes	Yes	No	---	---
Kalyanaram (2009)		√	√		2SLS (two stage least squares) regression model	Market share	Detailing + journal advertising (DTPP); DTCA	Retail price; competition intensity; avg cost per consumption	No	No	No	---	---

	Data aggregation		Level of analysis				Independent variables		Includes detailing…				
Author(s)	**Physician**	**Market**	**Brand**	**Category**	**Model**	**Dependent variable**	**Promotion tools**	**Other**	**Non-linear term?** (quadratic, log, or other)	**Lagged terms?**	**Stock / carryover?**	**Stock discount** (decay / wearout?*	**Monthly discount rate**
Narayanan & Manchanda (2009)	√		√		Hierarchical Bayesian structure in a Bayesian learning model	Sales (prescriptions)	Detailing	Patient requests	No	No	Yes	No	---
Fischer & Albers (2010)		√	√	√	Log-log model	Sales (prescriptions)	Detailing; journal advertising; DTCA	Drug price; order of entry; other variables	Yes	No	Yes	No	---
Fischer, Leeflang & Verhoef (2010)		√	√		Multi-level regression model	Level of peak sales; time-to-peak-sales	Detailing; journal advertising; direct mailing; competitive marketing activities	Order of entry; quality; number of new entries; drug price	No	Yes	Yes	Yes	54% (quarter)
Gönül & Carter (2010)		√		√	Multiple regression model	Sales (new prescriptions)	Detailing; e-detailing	Drug characteristics	No	No	Yes	Yes	0.4%
Leeflang & Wieringa (2010)		√	√		Modified Rizzo OLS regression model (Windmeijer, de Laat, Douven & Mot, 2006)	Sales (prescriptions)	Detailing; journal advertising; direct mail; competitive detailing	Drug price; competing drugs' avg price; drug age	No	Yes	Yes	Yes	N/A
Montoya, Netzer & Jedidi (2010)	√		√		Hierarchical Bayesian, nonhomogeneous hidden Markov model (1st) | Partially observable Markov decision process (2nd)	Sales (new prescriptions)	Detailing; samples	---	No	No	No	---	---
Nair, Manchanda & Bhatia (2010)	√		√		Descriptive linear regression model of prescription behavior	Sales (prescriptions)	Detailing	---	Yes	No	No	---	---
Dong, Chintagunta & Manchanda (2011)	√		√		Poisson-lognormal simultaneous equation model | Markov Chain Monte Carlo methods	Sales (new prescriptions)	Detailing; competitors detailing	---	Yes	Yes	Yes	No	---
Ching & Ishihara (2012)	√		√		Ordinary Least Squares (OLS) Regression	Sales (prescriptions)	Detailing; samples; detailing made by partner (co-marketing)	Price; clinical outcomes	No	No	Yes	Yes	4.1%
Dave & Saffer (2012)		√		√	Multiple regression model	Sales (prescriptions)	Direct-to-physician promotion (detailing + samples + journal advertising), DTCA	Price	Yes	No	No	---	---
Wieringa & Leeflang (2013)		√	√		Six models (including a modified Rizzo OLS regression model)	Sales (Defined Daily Doses)	Detailing; medical journal advertising; direct mail; competitive promotion expenditures	Drug age; drug age squared;	No	No	Yes	No	---
Ruiz-Conde, Wieringa & Leeflang (2014)		√		√	Trial–repeat diffusion models + Cross-sectional analysis	Sales (prescriptions)	Detailing; medical journal advertising; physician meetings; DTCA	---	Yes	Yes	Yes	No	---

	Data aggregation		Level of analysis				Independent variables		Includes detailing...				
Author(s)	**Physician**	**Market**	**Brand**	**Category**	**Model**	**Dependent variable**	**Promotion tools**	**Other**	**Non-linear term?** (quadratic, log, or other)	**Lagged terms?**	**Stock / carryover?**	**Stock discount** (decay / wearout?*	**Monthly discount rate**
Datta & Dave (2016)	√		√		Poisson regression model	Sales (new prescriptions)	Detailing; samples	Physician characteristics (age, gender, other)	Yes	No	Yes	Yes	20.0%
Kappe & Stremersch (2016)	√		√		Hierarchical Bayesian distributed lag model | Principal components analysis	Sales (prescriptions)	Detailing	---	No	Yes	Yes	No	---
Liu, Gupta, Venkataraman & Liu (2016)	√		√		Dynamic structural model of oligopoly competition in detailing (demand and supply), with 2-stage estimation + counterfactual simulations of detailing policy	Market share	Detailing	---	No	No	Yes	Yes	14.0%
Mukherji, Jaimakiraman, Dutta & Rajiv (2016)		√	√		Structural econometric model	Sales (prescriptions)	Detailing; DTCA	---	No	Yes	Yes	Yes	N/A
Chung, Kim & Park (2017)	√			√	OLS regression model	Sales (prescriptions)	Detailing; sampling	---	No	Yes	Yes	Yes	N/A
Kappe, Venkataraman & Stremersch (2017)	√		√		Multivariate Poisson regression model	Sales (prescriptions)	Detailing; competitors detailing	Trend; dummy (new product introduction)	No	Yes	Yes	No	---
Liu, Liu & Chintagunta (2017)	√		√		Hierarchical Bayesian logit model | Counterfactual policy simulations based on a dynamic oligopoly game of detailing	Sales (prescriptions)	Detailing; competitors detailing	---	No	Yes	Yes	Yes	1.0%
Shapiro (2018)	√		√		OLS regression model	Sales (prescriptions)	Detailing	Information shocks, patient characteristics	No	No	Yes	Yes	40.0%

Source: own elaboration

The analysis of the content of table 9.9 allows to conclude that a multitude of data models have been used by previous researchers. In the case of aggregated data (market aggregation), Rizzo (1999)'s model was adapted by Windmeijer, de Laat, Douven & Mot (2006), calibrating it to the Dutch pharmaceutical market.

Table 9.10 below summarizes the main advantages and limitations of Rizzo (1999) and Windmeijer et al (2006)' models.

Table 9.10 – Advantages and limitations of Rizzo and Windmeijer's models

	Advantages		Limitations	
Author(s)	**Main topics**	**Theoretical grounding (non-exhaustive)**	**Main topics**	**Theoretical grounding (non-exhaustive)**
Rizzo (1999)	Well accepted model, whose outcomes are globally interpreted as truths	Leeflang & Wieringa (2010)	Data was pooled (category level), assuming that the marketing effects of all brands have the same effect on demand	Leeflang & Wieringa (2010); Wieringa & Leeflang (2013)
	First author to analyze the effects of marketing expenditures on the price elasticity of pharmaceutical demand	Wieringa & Leeflang (2013)	Aggregated marketing expenditures	
	Impactful work on public policy makers opinions about the wellfare of the pharmaceutical industry promotional activities		European reality different from the USA's in terms of pricing definition (pricing in Europe is predominantly set by policy makers from government, industry, and insurance companies, and not directly set by pharmaceutical companies themselves	
			Incorrect assumptions of homogeneous parameters across brands	Wieringa & Leeflang (2013)
Windmeijer, de Laat, Douven & Mot (2006)	Adapts Rizzo's model to the Dutch market, in an application to the European reality	Leeflang & Wieringa (2010)	Also uses aggregated marketing expenditures	Leeflang & Wieringa (2010)
	More complete model than Rizzo's (included dummies for months and policy changes)		Data was pooled across 140 brands and 11 markets, which can lead to biased estimates	

Source: own elaboration

For the purpose of the empirical component of our research, we will follow Leeflang & Wieringa (2010) since, such as Leeflang & Wieringa (2010)'s data, our time series data of drug sales and detailing expenditures is characterized by aggregated data, at drug brand level, with drug sales as dependent variable, and a series of promotion instruments expenditures as independent variables (detailing, journal advertising, and other). As noted by Leeflang & Wieringa (2010), Rizzo's model, despite being well accepted, suffers from a few limitations listed in the table above. Such as in the Netherlands, in Portugal, prices are predominantely set by policy makers too (government), aspect which has been covered previously.

Interestingly, Leeflang & Wieringa (2010) are one of the few authors studying European-level time series of data, in the research community studying detailing and pharmaceutical marketing in general, as can be concluded from the articles examined in table 9.11, which characterizes the data origin of the selected perimeter of previous quantitative research on detailing.

Table 9.11 – Characterization of data origin from previous research on detailing

Author(s)	Country of origin of data	Sample (physicians)	Specialties	Drug class(es)	Drug brand(s)	Time series	Data sources
Parsons & Abeele (1981)	Belgium	N/A	N/A	Steroid group of prophylactic medicines for women	Anonymous	24 months	N/A
Mackowiak & Gagnon (1985)	USA	1,000-1,200	N/A	Benzodiazepines and diuretics	7 drugs (anonymous) in each class	60 months	IMS Health
Berndt, Bui, Reiley & Urban (1996)	USA	3,500	N/A	Antiulcer (H_2-antagonists)	Overall market	189 months	IMS Health
Rizzo (1999)	USA	N/A	N/A	Antihypertension	46 drugs	72 months	First Databank | The Physicians' Desk Reference | IMS Health | IMSPACT
Gönül, Carter, Petrova & Srinivasan (2001)	USA	157	Anonymous	Chronic condition among elderly	Anonymous	48 months	Scott-Levin Inc.
Wittink (2002)	USA	N/A	Primary care and specialties	Hypertension, asthma, arthritis, erectile dysfuntion, other	392 brands + 127 generics	72 months	Verispan (Scott-Levin Inc.) | ACNielsenHCI (PERQ/HCI)
Wosinska (2002)	USA	N/A	N/A	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	Baycol, Lescol, Lipitor, Mevacor, Pravachol, Zocor	41 months	IMS Health | Blue Shield of California | Competitive Media Reporting
Narayanan, Manchanda & Chintagunta (2003)	USA	N/A	N/A	Antihistamines	Claritin, Zyrtec and Allegra	105 months	Scott-Levin Inc.
Rosenthal, Berndt, Donohue, Epstein & Frank (2003)	USA	Multiple	N/A	Anti-depress., anti-hyperlipidemics, proton pump inhibit., nasal sprays, antihistamines	Several (25)	43 months	Marketing research firms | Competitive Media Reporting | Scott-Levin Inc | IMS Health
Manchanda & Chintagunta (2004)	USA	1,000	Specialists, primary care, and other (anonymous)	Mature product category	Anonymous	24 months	Pharmaceutical company (anonymous)
Manchanda, Rossi & Chintagunta (2004)	USA	1,000	Specialists, primary care, and other (anonymous)	Mature product category	Drug X (anonymous)	24 months	Pharmaceutical company (anonymous)
Mizik & Jacobson (2004)	USA	10,516 to 55,896	Anonymous	N/A	Anonymous	8 quarters	Pharmaceutical company (anonymous)
Narayanan, Desiraju & Chintagunta (2004)	USA	N/A	N/A	Antihistamines	Claritin, Zyrtec and Allegra	105 months	Verispan Inc
Chintagunta & Desiraju (2005)	USA UK Germany France Italy	N/A	N/A	Antidepressants	Prozac, Zoloft, Paxil	48 quarters	IMS Health | BLS | Eurostatistics
Narayanan, Manchanda & Chintagunta (2005)	USA	N/A	N/A	Antihistamines	Claritin, Zyrtec and Allegra	105 months	Verispan Inc | Pharmaceutical firms

Author(s)	Country of origin of data	Sample (physicians)	Specialties	Drug class(es)	Drug brand(s)	Time series	Data sources
Windmeijer, de Laat, Douven & Mot (2006)	Holland	N/A	General Practitioners	11 therapeutic classes	140 brands (anonymous)	72 months	Health Insurance Board | IMS Health
Berndt, Danzon & Kruse (2007)	15 countries	N/A	N/A	Antihypertensives, antidepressants and antiepileptics	Several	Up to 48 quarters	IMS Health
Venkataraman & Stremersch (2007)	USA	N/A	Several (N/A)	Statins, gastrointestinal and coagulation, and erectile dysfunction	4 brands (anonymous)	24 months	Pharmaceutical marketing firm | FDA | National Institute for Health and Clinical Excellence
Kalyanaram (2008)	USA	N/A	N/A	Anti-depressants, proton pump inhibitors, and antihistamines drugs	Several (14)	24 months	IMS Health | Competitive Media Reporting
Manchanda, Xie & Youn (2008)	USA	466	Specialists, primary care, and other (anonymous)	Chronic condition among 6% of the USA population	Drug X (anonymous)	34 months	IMS Health
Vakratsas & Kolsarici (2008)	Non-USA country	N/A	N/A	Lifestyle-related disease (anonymous)	3 brands (anonymous)	85 months	IMS Health
John (2008)	USA	N/A	N/A	N/A	Anonymous	8 quarters	Pharmaceutical company (anonymous)
Dong, Manchanda & Chintagunta (2009)	USA	330	Primary care	Proton pump inhibitor (gastroesophageal reflux)	Nexium, Prevacid, Aciphex, Protonix	12 quarters	ImpactRx
Kalyanaram (2009)	USA	N/A	N/A	Anti-depressants, proton pump inhibitors, and antihistamines drugs	Several (14)	24 months	IMS Health | Competitive Media Reporting | Cowen and Company, LLC
Narayanan & Manchanda (2009)	USA	900	General practitioners + Urologists	Erectile dysfunction	Viagra, Levitra, Cialis	9 months	ImpactRx
Fischer & Albers (2010)	USA	N/A	N/A	N/A	Several (2,831)	21 quarters	IMS Health | FDA
Fischer, Leeflang & Verhoef (2010)	France, Italy, Germany, UK	N/A	N/A	Calcium channel blockers and ACE inhibitors (antihypertensives)	Several (73), including Lipitor and Cozaar	31 quarters	IMS Health
Gönül & Carter (2010)	USA	N/A	N/A	6 classes	Several (21)	19 months	SDI Health | IMS Health
Leeflang & Wieringa (2010)	Holland	N/A	General practitioners + Psychiatrists	11 classes	Several (140)	N/A	N/A
Montoya, Netzer & Jedidi (2010)	USA	300	N/A	Medical condition in postmenopausal women	Anonymous	24 months	Pharmaceutical company (anonymous) + pharmacy audits

Author(s)	Country of origin of data	Sample (physicians)	Specialties	Drug class(es)	Drug brand(s)	Time series	Data sources
Nair, Manchanda & Bhatia (2010)	USA	1,500	N/A	Serious chronic disease that affects 1/4 of the US adult population	Anonymous	24 months	Pharmaceutical company | Market research firm
Dong, Chintagunta & Manchanda (2011)	USA	200	Primary care	Proton Pump Inhibitor (PPI) and antidepressants (AD)	8 brands	18 bi-months	ImpactRx
Ching & Ishihara (2012)	Canada	N/A	N/A	ACE inhibitor with diuretic (antihypertensives)	Vaseretic, Zestoretic, Prinzide	71 months	IMS Health
Dave & Saffer (2012)	USA	N/A	N/A	Analgesics / musculoskeletal, anti-lipidemics, gastrointestinal acid reducers, insomnia aids	Several (30)	144 months	Physicians' desk reference | Competitive Media Reporting | IMS Health
Wieringa & Leeflang (2013)	Holland	N/A	N/A	Ulcers, hypertension, cholesterol, depression, and asthma	84 brands	96 months	N/A
Ruiz-Conde, Wieringa & Leeflang (2014)	USA	N/A	N/A	Rhinitis, arthritis, asthma	Several (34)	96 months	Syndicated secondary data sources (anonymous)
Datta & Dave (2016)	USA	149,247	Dermatology, emerg. medicine, obst/gynec., primary care, other	Antivirals	Famvir	24 months	IMS Health + pharmaceutical market research firm
Kappe & Stremersch (2016)	USA	4,622	General practitioners + Specialists	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	Pravachol, Zocor, Lipitor, Crestor, Vytorin	96 months	IMS Health
Liu, Gupta, Venkataraman & Liu (2016)	USA	448	N/A	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	Lipitor, Zocor, Crestor, non-drug	24 months	ImpactRx
Mukherji, Jaimakiraman, Dutta & Rajiv (2016)	USA	N/A	N/A	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	Mecavor, Pravachol, Zocor, Lipitor	120 months	IMS Health
Chung, Kim & Park (2017)	India	9,595	Several (6)	Chronic pathology	Several	6 months	Pharmaceutical company (anonymous)
Kappe, Venkataraman & Stremersch (2017)	USA	1,585	General practitioners	HMG-CoA Reductase Inhibitors (Statins; cholesterol)	Lipitor, Zocor, Pravachol, Crestor	10 months	Narket research firm (anonymous)
Liu, Liu & Chintagunta (2017)	N/A	131	HIV specialists	HIV / AIDS	11 brands (including Atripla, Truvada, Norvir)	16 months	Marketing research firm (anonymous)
Shapiro (2018)	USA	2,031	General practitioners and psychiatrists	Antipsychotics	Seroquel, generic perphenazine	72 months	AlphaImpactRx

Source: own elaboration

Table 9.12 describes four of the models applied by Leeflang & Wieringa (2010). Models with pooled data are not present in the table, since in our dataset all data was organized at the individual brand level. All four models used logarithmized terms in both drug sales and independent variables (except for drug age and dummy variables). The models are described in table 9.12 below.

Table 9.12 – Summary of the research models

Model specification				Models applied by Leeflang & Wieringa (2010)			
				Wittink (2002) simplified	Wittink (2002) complete	Rizzo (1999)	Windmeijer et al (2006)
				Model 1	Model 2	Model 3	Model 4
Dependent variable				Drug sales in DDDs	Drug sales in DDDs	Drug sales	Drug sales in DDDs
Independent variables	Lagged sales		Ln Lagged sales period t-1	No	No	No	Yes
			Ln Lagged sales period t-2	No	No	No	Yes
	Marketing expenditures flow	Own	Ln Detailing flow	Yes	Yes	Yes	No
			Ln Detailing flow x Ln Detailing flow	No	No	Yes	No
			Ln Journal advertising flow	Yes	Yes	No	No
			Ln Direct marketing flow	Yes	Yes	No	No
			Ln Global marketing expenditures flow	No	No	No	Yes
		Competitive	Ln Competitive detailing flow	No	Yes	Yes	No
			Ln Competitive journal advertising flow	No	Yes	No	No
			Ln Competitive direct marketing flow	No	Yes	No	No
			Ln Competitive global marketing expenditures flow	Yes	No	No	Yes
	Marketing expenditures stock	Own	Ln Detailing stock	No	No	Yes	No
			Ln Detailing stock x Ln Detailing stock	No	No	Yes	No
			Ln Global marketing expenditures stock	No	No	No	Yes
		Competitive	Ln Competitive global marketing expenditures stock	No	No	No	Yes
	Price	Own	Ln Average drug price per DDD	Yes	No	Yes	Yes
		Competitors	Ln Average competitors drug price per DDD	No	No	Yes	Yes
	Drug age		Drug age	Yes	Yes	Yes	Yes
			Drug age^2	Yes	Yes	Yes	Yes
			Drug age^3	No	Yes	No	No
	Marketing expenditures interactions		Average drug price per DDD x Ln Detailing flow	No	No	Yes	No
			Ln Average drug price per DDD x Ln Detailing stock	No	No	Yes	No
			Ln Average drug price per DDD x Drug age	No	No	Yes	No
			Ln Journal advertising flow x Ln Detailing flow	No	Yes	No	No
			Ln Journal advertising flow x Ln Mailing flow	No	Yes	No	No
			Ln Mailing flow x Ln Detailing flow	No	Yes	No	No
			Ln Global marketing expenditures stock x Ln Average drug price per DDD	No	No	No	Yes
			Ln Global marketing expenditures stock x Ln Average competitors price per DDD	No	No	No	Yes
	Other		Year dummies	Yes	Yes	Yes	Yes
			Month dummies	Yes	Yes	No	Yes
			Policy change dummies	Yes	Yes	No	Yes

Source: own construction based on Leeflang & Wieringa (2010)

Multiplicative model

Following the great majority of the literature on the field of detailing and pharmaceutical marketing, and observing Leeflang & Wieringa (2010) option, we selected a multiplicative model, where we applied logarithms in both dependent variable (sales in DDDs) and independent variables (all promotion instruments, interactions, and other as later described in this thesis, except for drug age, dummies and percentage-based variables). In order to

overcome the problem with logarithm of zero expenditures (which happened in several promotion instruments, with zero investment in some months, especially in the digital promotion expenditures), we substituted all zero values by 1€ (logarithm of one equals zero).

Structural break models

A structural break can be defined as «*an instability or break in the parameters of the data*» (Valentinyi-Endrész, 2004; p. 12), as «*sudden events which change the structure of the econometric model under consideration*» (Maurya, Singh & Khare, 2016; p. 195).

As noted by Bai & Perron (2003), the literature on structural breaks includes both approaches to a single break, and to multiple breaks. Hansen (2001) explained several types of structural tests. One of these tests is a test for a structural break of unknown timing. Chow (1960), a pioneer in structural break models, developed a test for a structural break of known timing, by testing the equality of coefficients of two linear regressions splitting the sample in two periods. They then compared the sum of squares of the residuals assuming the equality versus inequality, using an F-test. The main limitation pointed to the Chow (1960) method is the fact that one must know, a priori, the timing of the break date, as noted by Hansen (2001), since otherwise the test may produce uninformative coefficients, and as a result the potentially true break data can be neglected. This limitation was addressed, as referred by Hansen (2001), when Quandt (1960) developed a test that foresaw the possibility of an unknown number of breaks, as an extension of Chow (1960)'s test. Quandt (1960)'s goal was to «*indicate various approaches to testing the hypothesis that no switch occurred in the parameters of a linear regression system against the alternative that one switch took place*» (p. 329).

Other type of structural break estimation consists of an estimation of the timing of a structural break, by obtaining confidence intervals for the break date, as explained by Hansen (2001). He noted that this can be achieved by least squares, where «*the least squares breakdate estimate is the date that minimizes the full-sample sum of squared errors*» (p. 121). Bai & Perron (1998) developed an estimation strategy aimed at constructing tests to identify estimates of the break dates, and the number of breaks, in the scope of a model where some of the parameters were not exposed to changes. They method allowed them to estimate successive break points in the data series. As a null hypothesis, they propose the inexistence of any structural break, versus an alternative hypothesis which foresaw the existence of an arbitrary number of structural breaks.

Previous research using structural breaks has already been applied to time series of data involving the Portuguese pharmaceutical market. Pita Barros & Nunes (2010) studied structural breaks using a monthly time series of pharmaceutical expenditure growth in Portugal, from January 1995 to August 2008. The method they selected for data analysis – a structural time series approach - considered both the number of structural breaks and their timing endogenously (unknown, or not defined arbitrarily), where data would speak for itself, highlighting potential structural breaks which were not assumed by the researchers. They then checked the timings against health policies adopted by the Health Ministry. They found evidence of two structural breaks, approximately around October 2005 and January 2007, whose timing corresponded to two compulsory price reductions. Pita Barros & Nunes (2010) noted that the method they observed may be especially applicable in the scope of unexpected policy changes, such as the ones that consecutively happened in the Portuguese health sector, with a series of 10 major policy measures concentrated in the period between the years 2002 and 2007. They reason that «*unexpected policy measures may produce an effect with a lag with respect to official dates*» (p. 441).

Given the specific characteristics of our research – existence of one very well identified break regarding detailing activities, in the form of a detailing ceiling which entered into force in August 2013, we followed Chow (1960)'s approach to identify significant changes in regression coefficients before and after the structural break. Two equations were used for each product: one using data before the entry into force of the 2013 detailing ceiling, and one using data after the 2013 detailing ceiling.

9.2.4. Qualitative phase

Table 9.13 below summarizes the research design applied in the qualiitative phase:

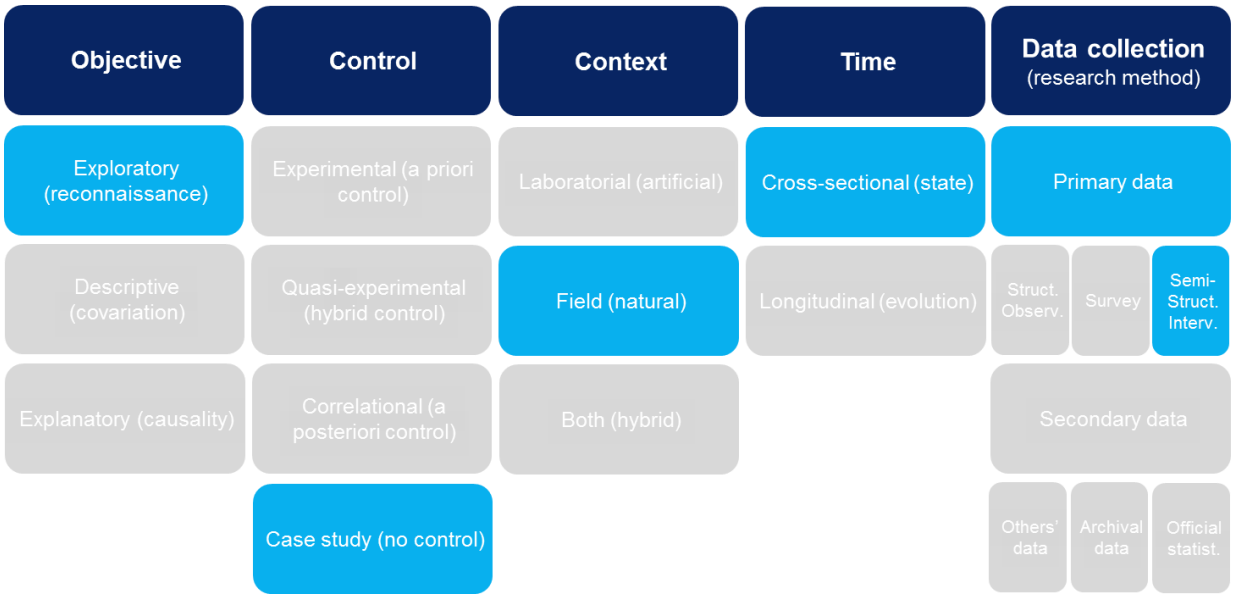


Table 9.13 - Research design scheme for the qualiitative phase

9.2.4.1.Research objective, control and context

In terms of the research objective, the research was exploratory in the second phase, to help understand why specific results have arised.

In this phase (qualitative), which had the goal of answering questions such as how or why, there was no control.

In terms of context, the qualitative phase was classified as field (natural), since it was conducted in the natural habitat, in the real world.

The selection of this research design (objective, control and context) for the qualitative – aimed at exploring insights on the behavior of healthcare professionals including physicians - was aligned with the designs used by authors like Prosser & Walley (2013a), Prosser & Walley (2013b), Grundy, Bero & Malone (2016), Skandrani & Sghaier (2016), and Saavedra, O'Connor & Fugh-Berman (2017), in the pharmaceutical marketing community.

9.2.4.2.Time

Concerning time, the research was cross–sectional (state) in the qualitative phase, since a single measurement in time was used.

9.2.4.3.Data collection

Primary research was generated in the qualitative phase, with the goal of probing quantitative results by exploring aspects of the central phenomenon (the moderating effect of a detailing ceiling on the relation between detailing intensity (measured through detailing flow) and prescription behavior (measured through sell-in sales in DDDs)), with a few participants from the pharmaceutical industry and policy regulators. The reason for following up with qualitative research in the second phase was to understand better and explain the quantitative results (Creswell, 2009).

9.2.4.4.Investigation strategy

Information from the quantitative phase was explored further using one case study consisting of the Portuguese pharmaceutical industry, with the goal of searching for converging evidence, making the outcomes as robust as possible.

The data collection **methods and tools** selected observed a triangulation goal, comprising semi-structured in-depth personal interviews, researchers' observations, documental analysis (pharmaceutical industry reports, regulator reports, pharmaceutical magazines, articles, legislation, other), and non-structured interviews with pharmaceutical marketing specialists.

The **actors**, or elements that provided information about the cases, observed a goal of triangulation, and included prescribers (physicians), influencers (pharmaceutical sales representatives), regulators, and others that allowed a better understanding of eventual specificities of the research results. Table 9.14 evidences the actors we planned to interview in the qualitative phase of the research. During fieldwork, in order to overcome some limitations, and to reach a broader perspective, we made minor changes to the list, as described later at the fieldwork process.

Table 9.14 – Planned interviewed actors

Scope	Stakeholder	Number of interviews
Government / Tutelage	Infarmed officer	1
	Former Ministry of Health (2011-2015)	1
	Former Ministry of Health (2015-2018)	1
Health Care Organizations	NHS ACES Director	1
	NHS Hospital Clinical Director	1
Health Care Providers	NHS exclusive General Practitioner (physician)	1
	NHS + Private Practice General Practitioner (physician)	1
	NHS exclusive Specialist (physician)	1
	NHS + Private Practice Specialist (physician)	1
Pharmaceutical Industry officers	General Manager	1
	Marketing / Sales Director	1
Pharmaceutical Sales Representatives	Pharmaceutical Sales Representative Market 1 - Blood	1
	Pharmaceutical Sales Representative Market 2 - Pancreas	1
	Pharmaceutical Sales Representative Market 3 - Heart	1
	Pharmaceutical Sales Representative Market 4 - Liver	1
		15

Source: own elaboration

Data analysis **technique** consisted of content analysis, performed using the software NVivo 11. A **case study protocol** was developed, defining the context and perimeter of questions for each case. A qualitative script was developed, subject to a pre-test and validation by the supervisor. In-depth interviews were made using sound recording (authorized by the interviewees), followed by interviews transcription to NVivo 11, finalizing with coding, analysis and interpretation.

9.2.4.5.Case study protocol

A case study protocol was designed, covering the general objectives of the research, the conceptual model and the type of paradigm used (pragmatism). The information of the interviewees was contextualized using a sociodemographic questionnaire, allowing the treatment and understanding of the information considered relevant, such as the personal, social, professional and academic context. The protocol also defined the requirements of identification of candidates for interview and ensured confidentiality of the entire interview

process. It was stipulated the use of a portable voice recorder to record the interviews and the perceptions or observations of the interviewer after each of the interviews.

Research goals

The case study was aimed at answering to the following questions:

- Which are the communication channels mostly used by the company to interact with physicians?
- And which are the promotion tools?
- What is the importance of detailing?
- Which were the goals of implementing a detailing ceiling?
- Was its implementation successful?
- Was its application on the field controllable? Is the control of the PSRs calls effective?
- Was there any structural change in the way PSRs contact with NHS institutions? Frequency, location of contact, booking new visits, …
- Did the industry react to the detailing ceiling? How?
- Were there any cases of misconducts / excess number of calls detected? Were there any consequences? Further measures taken?
- Was the policy considered sufficient to reach the proposed goals?
- Which changes would have to be made to make the ceiling more effective?

Context information

The context includes a series of relevant information that helped to understand each case. This information was collected in addition to the questions in the qualitative script, and included:

- **Market context** – the importance, both in terms of sales magnitude and sales growth, of each of the case studies
- **Social context** – the importance of the drugs (treatments), in the scope of public health, given the number of patients with pathologies treated by drugs in each of the cases
- **Economic context** – the context of austerity initiated after the financial assistance by Troika, which put a substantial pressure on the healthcare industry and overall economy

Field procedures

- **Credentials and Access to the Case Study Sites**

This section describes the processes that were observed so that data could be accessed.

- **Selection of eligible interviewees** – the first step consisted of the selection the roles, or positions, or responsibilities of the actors (before allocating names). The second step consisted of the identification of a series of candidates. Criteria defined for participants' selections was:

    - **Government / tutelage** – current and ex-government officers which were important actors in the definition of the 2013 detailing ceiling, and officers from INFARMED (the health authority supervising the registry, credentiation and identification of the PSRs

    - **Health care organizations** – officers or directors of ACES (groups of healthcare centers) and hospitals, the ones in charge of informing ARS (regional health administration) of PSRs non-compliance, according to Order 8213-B/2013, article 7

    - **Health care providers** - physicians working on the national health system (ACES, or groups of health centers, and hospitals). Two of the physicians with exclusivity to the NHS (one general practitioner and one specialist) and two with mixed practice (NHS and private)

    - **Pharmaceutical industry officers** – having an eligible function / occupation in the pharmaceutical manufacturer (PSR, or sales director / marketing director / general manager), commercializing drugs in one or more of the selected ATCs, and also Consultants

    - **Pharmaceutical sales representatives** – PSRs promoting products from the four markets' perimeters

- **Contact with eligible candidates** – contact was made by mobile phone, e-mail, informal networks (personal and professional contacts), social networks (Linkedin, Facebook), and face-to-face. In the first contact all candidates were given given specific details:

- The general objectives of the interview
- The reason for being contacted
- Probable duration of the interview (between 40 and 60 minutes)
- The need to record the interview with a portable recorder
- Confidentiality assurance
- The fact that interview transcripts would be sent for review and adding up any forgotten information

- **Meeting schedule** – whenever the invitations were accepted, a convenient location and date for the interview were set. Most of the interviews were set to Fridays

- **Interview** – all interviews were conducted by the PhD candidate, using a portable sound recorder. In order to properly manage the interview dynamic in terms of sequence, content and homogeneity among all interviews, a previously developed qualitative script was used

- **Post-interview** – after each interview, the PhD candidate recorded his perceptions, first ideas, and unanswered questions for each interview. These preliminary first insights about the dynamic conducted happened to be of substantial value during the content analysis phase, helping to understand the context and support both the hand-written notes and the interviews transcriptions, for a holistic approach

- **Information sources**
  - Non-structured interviews with pharmaceutical industry specialists
  - Semi-structured in-depth interviews with pharmaceutical industry stakeholders
  - Legislation
  - Other (including industry publications and articles)

- **Procedural reminders**
  - **Communication channel used for the interaction** – whenever a face-to-face meeting was rejected (due to lack of availability of the interviewee), a

telephone interview was proposed, as an alternative. A third alternative as the last contingency plan was to request written answers to a set of questions sent by mail, by the researcher

- **Confidentiality issues** – all interviewees were given confidentiality assurance that information (documents, photos, video, and sound) gathered during the interviews would be kept confidential. This assurance was given at the beginning of the interaction, before starting the interview. A non-disclosure agreement would be given to the interviewees, if requested

- **Usage of digital recorder** – a smartphone was used to record all interviews

- **Procedures used for transcription and double-checking by interviewees** – after the completion of the interviews phase, transcriptions were performed by the researcher, and sent to interviewees for validation

- **Content analysis software** – NVivo 11 was used to record and monitor all research (content analysis). NVivo 11 was used as well to perform data analysis with increased accuracy, from the very beginning of the research

- **Documenting research steps** – all research steps after the beginning of the qualitative phase were documented in a research diary, which included:

  - Entry dates of the note

  - Title of the note

  - Notes – these notes included insights written after the interviews, information found in different channels (such as videos, news, and other considered relevant) and researcher's feelings and vents, and perceptions about the research

Preliminary Guidelines for Case Study Data Collection

- **Specific issues to remember during data collection**

A specific interview script was built for each of the five types of interviewee. This script included a set of pertinent questions, in order to obtain answers and insights.

The script contains primary questions, and secondary or optional questions (one or two per dimension). These secondary questions were activated whenever the researcher needed more precision and clarity in the answer, namely in the following situations:

- Interviewees only gave limited information;
- Interviewees had some difficulties expressing themselves;
- Non-verbal language did not match the expressed answers given.

Examples of such secondary questions include "How did you feel about this situation?", "Could you have decided differently?", or "How exactly did you do it?".

A maximum of 6-7 questions was applied in each script dimension (sum of primary and secondary questions).

In the semi-structured interviews, where only open-ended questions were used, the researcher was prepared to have included other questions adding value and insights to the formal questions present at the script. In this situation, the funnel technique was applied, where global, general questions were asked first, and specific, detailed questions were put later in the sequence.

The researcher recorded the information collected in the interview by handwriting (general ideas) and complemented with digital voice recording, whever allowed by the interviewees. A transcript was done as soon as possible after the interview (after a maximum of up to two weeks), as well as a memo recording the personal comments of the researcher based on observation during the interview. As referred previously, the transcripts were sent to interviewees for review, adding up any forgotten information, and approval.

Tables for data collection and possible information sources to answer each research question

Data collection was separated as follows:

- Contextual data – the topic included personal, professional and academic, and social data, helping the researcher to know each interviewee general profile
- General data – in this topic, a definition for each dimension was created, as well as the specific questions in each dimension

Contextual data

Table 9.15 evidences the contextual data.

Table 9.15 – Contextual data – qualitative research

Context area	Unit	Questions	Possible information sources
Personal	Age	Age interval	Linkedin (based on year of graduation)
Professional and academic	Profession	Profession occupation	Linkedin / Search engines / Personal network / interviewee
	Academic	Academic qualifications	

General data

Tables 9.16, 9.17 and 9.18 represent the general data table, where we list the macro dimensions, the units (or sub-dimensions), the concepts definition, the targets, and the questions themselves. It started with macro dimension 1 – Pharmaceutical communication channels and promotion tools.

Table 9.16 – General Data – Dimension 1

Macro dimension	Unit (or Sub-dimension?)	Concept definition	Target (stakeholders)	Questions
Pharmaceutical communication channels and promotion tools	Communication channels	Means or vehicles through which the message moves from the sender to the receiver	All	1) Given your experience in the health sector, which are the most common communication channels used by pharmaceutical companies to vehiculate their messages to physicians? (face-to-face, on-line, telephone, mail, ...) 2) Considering the last five years, do you see any pattern change in terms of channels used? If so, why do you think that happened?
	Promotion tools	Instruments used by companies to develop interactions with clients and reach promotion goals, using communication channels	All	3) And which are the most common promotion tools used by pharmaceutical companies to interact with physicians? 4) Do you see any pattern change in the utilization of promotion tools, in the last 5 years? If so, why do you think that happened?
	Effect of promotion tools on prescription behavior	Impact of promotion tools on physicians prescription behavior	All	5) In your opinion, what are the main goals of pharmaceutical companies when they decide to use promotion tools to interact with physicians? 6) Do you believe the promotion tools used by pharmaceutical companies can influence physicians' prescription choices? Why? How? To which extent? In which occasions / situations? 7) As you know, companies typically use a series of promotion tools including visits made by pharmaceutical sales representatives, activity also know by detailing, mailing, journal advertising, e-detailing, medical meetings, congresses, and other. How would you set the ranking of these instruments in their ability to influence doctors' prescribing decisions? (No. 1 = instrument with greater capacity of influence, No. 2 = instrument with second greater capacity of influence, etc). Why did you set the ranking this way? 8) In your view, what is the importance of detailing to pharmaceutical companies? And to the physicians? Is this importance equal for new vs older drugs? And is it equal for original drugs vs generics? 9) In your opinion, which are the main factors influencing physicians prescription decisions?
			Physicians only	10) Do you consider that detailing influences your prescription decisions? To which extent? Why? 11) Do you consider yourself less or more easily influenced than your colleagues, concerning the effect of detailing on prescription decisions? Why?

Source: own elaboration

We then moved to dimension 2 – Implementation of the detailing ceiling in the National Health System

Table 9.17 – General Data – Dimension 2

Macro dimension	Unit (or Sub-dimension?)	Concept definition	Target (stakeholders)	Questions
Implementation of the detailing ceiling in the NHS	Motivations and goals of the detailing ceiling	Motivations and objectives of the tutelage for the detailing ceiling	All	12) In your view, what was the main goal the tutelage wanted to attain when it decided to limit the number of visits PSRs can make to NHS doctors and institutions? 13) Do you believe there other additional goals for imposing that limit?
	Implementation of the detailing ceiling	Process of implementation, on the field, of the detailing ceiling	All (adjust to "in your institution" in the case of NHS institution directors)	14) In your view, was the detailing ceiling to the NHS adequately implemented on the field? To which extent? Why do you think that? 15) Was the application of the ceiling to the NHS controlable, that is, was it simple to control whether the PSRs observed the maximum number of visits allowed? Why do you think that? How was the control made? 16) (Adjust in the case of NHS institution directors) To the extent of your knowledge, were there any cases of misconduct / excess number of visits detected? Were those eventual cases reported? Were there any consequences? Were there further measures taken?
	Pharmaceutical companies reaction	Reaction of the pharmaceutical companies to face the entry into force of the detailing ceiling	All	17) Did pharmaceutical companies react to the detailing ceiling imposed to the number of visits to the NHS? How? When? 18) Did pharmaceutical companies use any "tricks" to circumvent the ceiling to the number of visits to the NHS? Which? Did it produce results? (ex: additional companies with different VATs, visiting doctors at their private practice, …)

Source: own elaboration

Dimension 3 – Effect of the detailing ceiling to the NHS is shown below.

Table 9.18 – General Data – Dimension 3

Macro dimension	Unit (or Sub-dimension?)	Concept definition	Target (stakeholders)	Questions
Effect of the detailing ceiling to the NHS	On PSRs	Effect of the detailing ceiling on PSRs activity	All	19) In your view, was there any structural change in the way PSRs interacted with NHS institutions, as a consequence of the entry into force of the detailing ceiling, comparing with the previous reality? In the average number of visits made per day, in the frequency, location of contact, booking of new visits, ...? Any "trick" used by the PSRs? How did PSRs adjust to the detailing ceiling to the NHS?
	On pharmaceutical companies	Effect of the detailing ceiling on pharmaceutical companies promotion decisions	All	20) In your view, did pharmaceutical companies reallocate its investments in promotion tools, due to the entry into force of the detailing ceiling to the visits made to the NHS? Ex: less investment in detailing and more investment in other promotion tools? Which ones?
	On NHS institutions	Effect of the detailing ceiling on the activity of the NHS institutions	All	21) Do you think there was an impact on NHS institutions' daily activity as a result of the limitation of the number of visits made by the PSRs? Can you please elaborate?
	On NHS physicians	Effect of the detailing ceiling on the activity of NHS physicians	All (adjust to "you" / "your" in the case of physicians)	22) Was there any impact on NHS physicians as a result of the limitation of the number of visits made by the PSRs? If any, was it positive or negative? Why? 23) (Adjust in the case of Physicians) And was there any structural impact on physician prescription behavior due to the entry into force of the detailing ceiling to visits to the NHS? If so, which impact? Why?
			All	24) Do you consider that the detailing ceiling impacted all pharmaceutical companies the same way? Why? Ex: companies with higher detailing intensity vs companies with lower detailing intensity
	Goals attained	Ability of the detailing ceiling to reach the tutelage goals	All	25) Do you believe the detailing ceiling had a real impact on the field, translated into an effective reduction in the number of PSRs visits to NHS doctors and institutions? Why? To what extent? 26) Globally, do you consider that the ceiling to the number of PSRs visits to NHS reached the tutelage goals? Why?
	Adjustments to the detailing ceiling	Eventual adjustments to the detailing ceiling to make it more effective	All (adjust in the case of the NHS officer in charge in 2013)	27) (Adjust in the case of the NHS officer in charge in 2013) Imagine you had the opportunity to design this detailing ceiling to the number of visits to the NHS, back in 2013. Would you have done something differently? Why? How? With different limits? With a different approach?
	Final comments	Final comments the responder wants to make	All	28) Would you like to make any final comments?

Source: own elaboration

Preliminary Outline for the Case Study Report

The information included in the case study report was reviewed iteratively, in the sense that there was evolution and review until it was considered to have achieved a satisfactory level of quality to allow transmitting the desired messages with clarity and reasonable objectiveness.

The case study report passed through the steps mentioned by Lincoln and Guba (1985): explain the problem under study, depict with clarity and rigor the applicable context, describe the activities and processes observed within that context, emphasize the aspects studied in detail on each site, and present the key insights of the research.

9.2.5. Critical analysis of the chosen methodology

The selected methodology incorporates several potential limitations and strengths, summarized below.

Regarding promotion data, and depending on the therapeutic classes, drugs and medical specialties selected for analysis, statistical reliability may be lower than the global expected 4,35% for a confidence interval of 95%. Nevertheless, sales data, collected from distributors in the Portuguese market, represents at least 95% of the market sales in Portugal.

Concerning internal validity, there were several government policies (not related to restrictions to detailing activity) that took place. If some of them most likely did not have substantial effects during the time series period (January 2012 to December 2015), such as as compulsory price reductions in both brands and generics (especially between 2005 and 2010), others may have had non-insignificant impacts, such as the entry into force of compulsory writing of prescriptions by international nonproprietary name (INN, which took place in 2012, limiting the ability of physicians to prescribe using the brand names of medicines, given that generics are available), troika intervention causing severe budget constraints in health management (reducing market sales), economic crisis (which may have led to reductions in the number of PSRs, reducing the number of sales calls to physicians), and other. However, the quantitative analysis model tested some of the incorporation of qualitative variables in order to isolate their effects on the dependent variable (prescription behavior). Also, the fact that four therapeutic classes were selected (two less impacted by generics, and two more impacted) contributed to the increase in robustness of internal validity. Another relevant aspect that may impact internal validity is the possible impact of contaminating variables such

as the levels of expectations and the sales potential, which may have impacted the pharmaceutical companies' decisions on the sales force sizing and number of visits to physicians. The qualitative phase of the research helped however to analyze and mitigate this possible impact on internal validity.

Despite the limitations above, we believe the proposed research was adequate when assessed from additional perspectives. The first is external validity. Despite the fact that most of previous research was conducted using US–based data, the current research has relevant external validity, since data source, data, methods and strategy to answer to the research question are similar to the ones applied by previous researchers. The second is measurement validity. The proposed research is aligned with what experts in the pharmaceutical marketing and detailing have been studying (content validity), and addressed the same variables using longitudinal data and a case study (construct validity). The third is reliability (or replicability). Despite the fact that it was not possible to guarantee full reliability, since results in the literature reveal a certain extent of variability (especially in the magnitude of the relation), the proposed research used the same data source, the same variables and the same data aggregation as a substantial community of researchers in pharmaceutical marketing, and the analysis model will be inspired on previous research by other authors. Also, the proposed research applied the same analysis model to a long time series, testing whether the results are coherent over time (test and re–test).

Focusing on the qualitative phase, the research benefited from construct validity (since several information sources were used, and the interview transcriptions were reviewed by the participants), external validity (since the research was linked to similar research already conducted) and reliability (since a case study protocol was developed, data was stored and treated, all steps were recorded and data was organized and catalogued).

10. Empirical study - quantitative

This chapter starts by exploring the data procedures observed to prepare data for analysis. It then explores the application of several models used by Leeflang & Wieringa (2010). Finally, it explored adaptations of those models by including new variables. Conclusions were then addressed at the end of the chapter.

Important decisions were taken regarding the analysis model application. These involved the inclusion of lagged analysis, non-linear terms, detailing stock (carryover), detailing stock discount, and the detailing stock discount monthly value, later explored in this chapter.

10.1. Data preparation procedures

Some procedures were performed regarding IQVIA data, which will be explored in the following sub-chapters.

10.1.1. Data extraction

Sell-in data was extracted using Dataview software, regarding the markets defined. Since Dataview only provides information of a maximum of three years, four CSV files were extracted: January 2006-December 2008, January 2009-December 2011, January 2012-December 2014, and January 2015-December 2017. The four CSV files were then merged into one single file. Promotion data was extracted from Channel Dynamics into an EXCEL file. IQVIA Portugal only had monthly data regarding promotion investments from January 2012, and as a consequence the analysis period was focused on the 19 months before the entry into force of the detailing ceiling (from January 2012 to July 2013), and the 29 months after (from August 2013 to December 2015). Promotion data was then incorporated into the sell-in merged dataset, mostly by automatic procedures (with a small number of drugs matched manually).

10.1.2. Dataset configuration

The received dataset had several megabytes of information, which was then compiled in order to feed the data analysis step. A new configuration was prepared, which had the structure shown below in table 10.1.

Table 10.1 - Dataset adjusted configuration – Sell-in data

	Drug X								
	Sales (sell-in)		Other information						
Month	Units	Values €	Pack	Counting units	Retail selling price	Drug authorization date	Drug launch data	Molecule	ATC3
Jan 2012	Q	€	String	Q	€	month/year	month/year	String	String
Feb 2012	Q	€	String	Q	€	month/year	month/year	String	String
Mar 2012	Q	€	String	Q	€	month/year	month/year	String	String
…	Q	€	String	Q	€	month/year	month/year	String	String
July 2013	Q	€	String	Q	€	month/year	month/year	String	String
Aug 2013	Q	€	String	Q	€	month/year	month/year	String	String
…	Q	€	String	Q	€	month/year	month/year	String	String
Oct 2015	Q	€	String	Q	€	month/year	month/year	String	String
Nov 2015	Q	€	String	Q	€	month/year	month/year	String	String
Dec 2015	Q	€	String	Q	€	month/year	month/year	String	String

Source: own elaboration

Promotional data was also adjusted into a new configuration, here shown below in tables 10.2 and 10.3.

Table 10.2 - Dataset adjusted configuration – Promotion data

	Drug X													
	Promotion investments data													
	Traditional channels								Digital channels					
Month	Tele-detailing	Face to face detailing	Face to face detailing	Mailing	Drug samples	Meetings	Journal advertis.	Clinical trials	E-detailing (automated)	E-detailing (remote with rep)	Meetings (automated)	Meetings (live)	Corporate Website	E-mailing
Jan 2012	N	N	€	€	€	€	€	€	€	€	€	€	€	€
Feb 2012	N	N	€	€	€	€	€	€	€	€	€	€	€	€
Mar 2012	N	N	€	€	€	€	€	€	€	€	€	€	€	€
…	N	N	€	€	€	€	€	€	€	€	€	€	€	€
July 2013	N	N	€	€	€	€	€	€	€	€	€	€	€	€
Aug 2013	N	N	€	€	€	€	€	€	€	€	€	€	€	€
…	N	N	€	€	€	€	€	€	€	€	€	€	€	€
Oct 2015	N	N	€	€	€	€	€	€	€	€	€	€	€	€
Nov 2015	N	N	€	€	€	€	€	€	€	€	€	€	€	€
Dec 2015	N	N	€	€	€	€	€	€	€	€	€	€	€	€

Source: own elaboration

Table 10.3 evidences a series of additional variables contained in IQVIA's database, related to detailing.

Table 10.3 – Other promotion detailing-related data - Promotion data

	Drug X					
	Other promotion detailing-related data					
Month	Visit duration	Nr of promoted products	Interest of the contact	Current prescription level	Future prescription intention	Visual aid delivered
Jan 2012	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
Feb 2012	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
Mar 2012	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
…	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
July 2013	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
Aug 2013	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
…	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
Oct 2015	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
Nov 2015	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N
Dec 2015	Minutes	N	Multiple response	Multiple response	Multiple response	Y/N

Source: own elaboration

10.1.3. Variables description

We now characterize each of the available variables in the dataset provided by IQVIA, in tables 10.4 and 10.5.

Table 10.4 – Sell-in variables description

	Type	Description
Sales in units	Numeric	Sell-in units
Sales in counting units	Numeric	Number of pills or treatment units (tablets, capsules) in each pack (ex: 30 pills)
Sales in Euros	Numeric	Sell-in sales in Euros
Pack	String	Description of the pack size (ex: 10mg)
Retail selling price	Numeric	Price the patient pays at the pharmacy, in Euros
Drug authorization date	Date	Date on which the marketing authorization was granted (month and year)
Commercialization date	Date	Date on which the drug was first commercialized in the market (month and year) (can be different from the drug authorization date)
Molecule	String	Name of the corresponding molecule
ATC3	String	Name of the corresponding Anatomic Therapeutic Chemical (ATC) code

Source: own elaboration

Table 10.5 – Promotion variables description

		Type	Description	Levels
Traditional channels	Tele-detailing	Numeric	Amount spent with tele-detailing (telephone) calls promoting the drug (in Euros)	---
	Face to face detailing (visits)	Numeric	Number of detailing visits promoting the drug	---
	Face to face detailing (Euros)	Numeric	Amount spent with the detailing visits promoting the drug (in Euros)	---
	Mailing	Numeric	Amount spent in mailing (regular mail) investments (in Euros)	---
	Drug Samples	Numeric	Amount spent in drug samples (in Euros)	---
	Meetings	Numeric	Amount spent in meetings (assumes more than one physician impacted), face to face (in Euros)	---
	Journal advertising	Numeric	Amount spent in ads posted in printed medical journals (in Euros)	---
	Clinical trials	Numeric	Amount spent in clinical trials involving the drug (in Euros)	---
Digital channels	E-detailing (automated)	Numeric	Amount spent with virtual (self) e-detailing promoting the drug (in Euros)	---
	E-detailing (remote with rep)	Numeric	Amount spent with video (live) e-detailing promoting the drug (in Euros)	---
	Meetings (automated)	Numeric	Amount spent in meetings in digital channels, with no personal interaction (in Euros)	---
	Meetings (live)	Numeric	Amount spent in meetings in digital channels, with personal interaction, remotely (in Euros)	---
	Corporate Website	Numeric	Amount spent in corporate websites (more applicable to OTC products) in Euros	---
	E-mailing	Numeric	Amount spent in e-mailing (electronic mail) investments (in Euros)	---
Other promotion detailing-related data	Number of products	String	Number of products promoted during the call	1, 2, 3, >3
	Interest of the contact	String	Physician evaluation of the interest of the contact, considering its usefulness to his or her medical practice	Not at all useful nor of value to your practice Somewhat useful and of value to your practice Very useful and of value to your practice DK/DA
	Current prescription level	String	Current declared prescription level of the promoted drug	Never New to me thus never prescribed Occasionaly Lapsed user Frequently DK/DA
	Future prescription intention	String	Future declared prescription intention of the promoted drug, based on the detailing visit	Decrease / stop Remain unchanged Increase / will begin to prescribe DK/DA
	Visual aid type	String	Existence of any visual aid during the interaction with the physician	No Yes (Ipad / Tablet) Yes (laptop-based material) Yes (printed material) DK/DA

Source: own elaboration

10.1.4. IQVIA variables subject to transformation

Some of the variables provided by IQVIA had to be transformed as a preparation step for the data analysis.

10.1.4.1. Drug sales

IQVIA data contains, as seen above, drug sales in Euros, valued at the wholesaler price, also called sell-in price, consisting of the price wholesalers charge to pharmacies. Since the selected markets and products consist of prescription drugs, this variable represents physicians' prescriptions of those drugs. IQVIA database also includes sales in units and in counting units. Counting units consist of the number of pills or treatment units (tablets, capsules) in each pack. For instance, one pack of Drug X 10mg 30 pills represents one Drug X 10mg units sold, but 30 counting units sold. However, there was the need to use a dependent variable that was immune to drug prices and to different pack sizes, which consisted of the defined daily doses (DDD), a unit of measure that represents the assumed average daily dose of maintenance therapy of a certain active substance in its main therapeutic indication in adults, and that does not necessarily reflect the dose the physician prescribed, acccording to the WHO Collaborating Centre for Drug Statistics (2018), option also followed by Windmeijer, de Laat, Douven & Mot (2006) and Leeflang & Wieringa (2010). Leeflang & Wieringa (2010) explained that DDD is a «*standard measure to compare drug use across different drugs*» (p. 124). The WHO Collaborating Centre for Drug Statistics (2018) also explained that «*DDDs provide a fixed unit of measurement independent of price, currencies, package size and strength enabling the researcher to assess trends in drug consumption*». According to the World Health Organization, the advantages of using DDD also include the evaluation of the effect of an intervention on drug use, and evaluate the regulatory impact and impacts of interventions on prescription patterns (WHO, 2018).

The process that was observed to convert sales in units into sales in DDD was the following:

- First, we consulted the WHO Collaborating Centre for Drug Statistics (2018) website https://www.whocc.no/atc_ddd_index/, where we could search for the DDD of the drug brands included in the analysis perimeter. By inserting the ATC3, we had access to the DDD. We provide an example below (fugure 10.1):

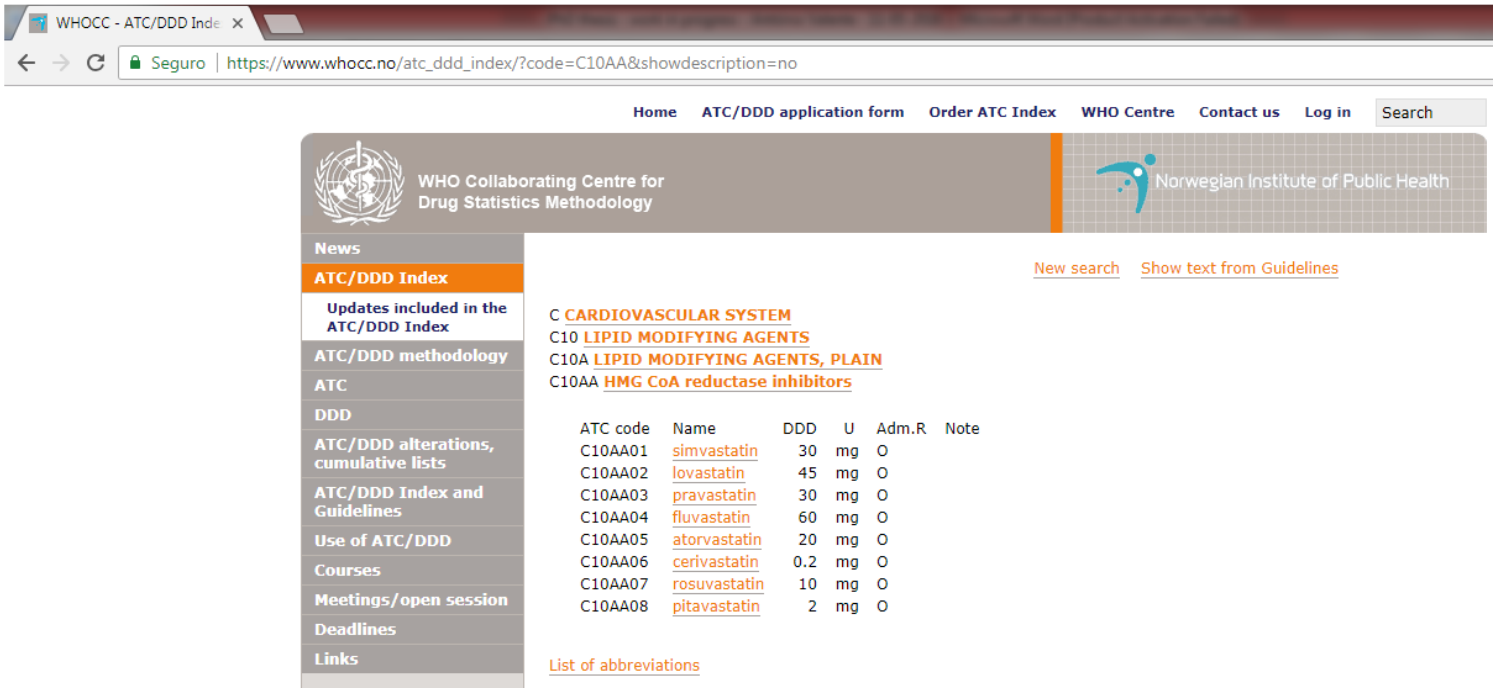


Figure 10.1 - Screenshot of ATC/DDD index

- Second, we created an EXCEL spreadsheet where, using DDD values established by the World Health Organization, we converted IQVIA's sell-in data (which consisted of the number of packs sold of each drug, and the number of dose units in each pack) into sell-in DDDs. We provide an illustrative example for an hypothetical product (here called product X), shown below in table 10.6:

Table 10.6 – Product X DDDs

DDD	Unit
20	mg

Since product X has many presentations, we needed to calculate the DDDs for each of its presentations.

Table 10.7 explicits the calculations made to compute both the DDDs and the average price for product X, in a given month.

Table 10.7 – Calculation of DDD and average price for product X

								Windmeijer et al (2006)
Product presentations	Number of pills per box	Mg per pill	Sales in Month 1 (nr of boxes)	Total dosage of the presentation in month 1	DDDs equivalents	Quocient to apply to the database, to calculate DDDs	Sales in Euros (wholesale)	Avg price per DDD
Presentation 1	30	10	150	45.000	2.250,0	15,0	8.500 €	3,78 €
Presentation 2	28	20	20	11.200	560,0	28,0	1.950 €	3,48 €
Presentation 3	42	15	45	28.350	1.417,5	31,5	4.750 €	3,35 €
Presentation 4	10	10	250	25.000	1.250,0	5,0	9.000 €	7,20 €
Presentation 5	28	15	200	84.000	4.200,0	21,0	15.000 €	3,57 €
Presentation 6	14	15	30	6.300	315,0	10,5	2.000 €	6,35 €
					9.992,5		**41.200 €**	**4,12 €**

Source: own elaboration

By multiplying the mg by the number of days of treatment and by the number of boxes sold in each presentation, we obtained the total dosage of the presentations sold. As an example, in the first row product X sold 150 boxes of 30 tablets, each one with 10mg. This is equivalent to 45 thousand mg, or 2.250 DDDs (45.000 / 20). By summing all the DDDs equivalents, we get the number of DDDs that should be put in the sales database (9.992,5 DDDs for Month 1), for product X.

Some of the products consisted of a fixed combination of two active principles. In these cases, the WHO Collaborating Centre for Drug Statistics website did not set a DDD. To solve this, we looked at the DDDs for each of the active principles, and considered one of the two as the DDD for the combination therapy. Calculations were set relative to the selected principle (ex: Product A is a combination of 50mg active principle 1 and 5mg active principle 2. DDD for principle 1 is 50mg per day and DDD for principle 2 is 5mg per day. We guaranteed consistency between the selection of the unit magnitude (mg relative to one of the principles, and DDD relative to that specific principle). This option did not provoke any bias to the results, given that all applicable products were given the same DDD calculation method. Aplicable products where this treatment was performed were:

- Market 2 – Pancreas – four products and two competitors
- Market 3 – Heart – five products and one competitor
- Market 4 – Liver – two products and one competitor

10.1.4.2. Drug price

Data provided by IQVIA included the wholesale and the retail selling price of the drugs. More than one approach could be observed in respect of the drug price. For instance, Leeflang & Wieringa (2010) divided the costs by the volume of sales, and obtained an average drug price in Euros, and Windmeijer et al (2006) calculated a price per DDD, by dividing the total cost by the total number of DDDs prescribed per month. We selected Windmeijer et al (2006)'s approach, which allowed us to have both sell-in sales and average drug price in DDDs.

To calculate the average price per DDD for product X, we divided the sum of sales in Euros by the total DDDs, in the case 41.200€ / 9.992,5 DDDs = 4,12€ average price per DDD. This can be seen in table 10.7 above.

10.1.4.3. Average competitors' price

Average price per DDD of competing drugs was calculated accordingly. We divided the sum of the sales in Euros by the sum of the sales in DDDs, obtaining the average competitor price per DDD.

10.1.4.4. Competitive detailing

IQVIA's database includes, as seen before, detailing activities in units (number of calls detaiing a specific product) and Euros for all therapeutic classes selected for analysis. Since detailing activities were available for all brands in each therapeutic class, two variables could be prepared:

- Detailing for each brand, also called detailing flow - given by the monthly investments in detailing, of each brand
- Competitive detailing - given by the sum of the detailing activities performed by competitors of a specific drug (in each market, a perimeter of drug brands was selected as previously explained, and the competitive detailing is the sum of detailing activities of those brands)

Table 10.8 below illustrates a simplified example of detailing flow and competitive detailing.

Table 10.8 – Illustration of detailing flow and competitive detailing

	Nr of details in a given month	
Drug A	100	→ Detailing flow for drug A
Drug B	50	
Drug C	150	275 → Competitive detailing for drug A
Drug D	75	

Source: own elaboration

For the calculation of the competitive detailing for each brand, we summed the detailing activities of the brands that were considered as main competitors, as described before in the topic **Brands' selection in each market**.

10.1.4.5. Stock variables

Detailing stock was calculated following Narayanan, Manchanda & Chintagunta (2005) and Manchanda, Xie & Youn (2008) approaches, considering a montly discount rate of 30%, to represent the depreciation or decay of the detailing effectiveness over time. This means, as noted by Narayanan, Manchanda & Chintagunta (2005), that after six months, the impact of expenditures on detailing have diminished by almost 90%. This was calculated by computing $(1\text{-}0,3)^6 = 0,118$. If we then calculate 1 – 0,118 we get 88,2%, which is close to the reported 90%. After 12 months, the impact of detailing has diminished 98,6%. According to Narayanan, Manchanda & Chintagunta (2005), this carryover discount rate is consistent with belief of pharmaceutical industry practitioners. This is quite an "aggressive" carryover discount rate, since other authors have used lower percentages (such as Windmeijer, de Laat, Douven & Mot, 2006; Ching & Ishihara, 2012; Liu et al, 2016).

Narayanan, Manchanda & Chintagunta (2005) also used a monthly discount rate for other marketing expenditures (OME) of 30%, which we also used in our analysis.

Table 10.9 illustrates the impact of the carryover discount rate, for visualization purposes (values do not represent actual values, and are shown for visualization purposes only).

Table 10.9 – Illustration of the calculation of own detailing stock

Carry-over monthly discount rate set at	30,0%

Time lags (in months)	Depreciation factor	Effectiveness loss
12	1,4%	98,6%
11	2,0%	98,0%
10	2,8%	97,2%
9	4,0%	96,0%
8	5,8%	94,2%
7	8,2%	91,8%
6	11,8%	88,2%
5	16,8%	83,2%
4	24,0%	76,0%
3	34,3%	65,7%
2	49,0%	51,0%
1	70,0%	30,0%

	Detailing flow for drug A	Detailing stock for drug A
January 2012	500	---
February 2012	600	---
March 2012	700	---
April 2012	700	---
May 2012	800	---
June 2012	700	---
July 2012	400	---
August 2012	300	---
September 2012	500	---
October 2012	600	---
November 2012	700	---
December 2012	400	---
January 2013	350	1216,9
February 2013	450	1092,0
March 2013	500	1073,6
April 2013	500	1094,7
May 2013	600	1109,5
June 2013	600	1188,9
July 2013	350	1245,5
August 2013	250	1112,9
September 2013	300	951,2
October 2013	400	871,0
November 2013	500	883,9
December 2013	250	961,9

Source: own elaboration

In this example, the detailing stock of January 2013 was calculated as 500 x 1,4% + 600 x 2,0% + 700 x 2,8% + 700 x 4,0% + 800 x 5,8% + 700 x 8,2% + 400 x 11,8% + 300 x 16,8% + 500 x 24% + 600 x 34,3% + 700 x 49,0% + 400 x 70,0% = 1.216,9.

Since our time series dataset started in January 2012 (19 months before the entry into force of the detailing ceiling), this implies that we would only have seven full monthly observations with stock variabels (January 2013 to July 2013, before the entry into force of the ceiling), which might have limited the robustness of the analysis. Therefore, we had two alternative options:

- The first was to follow Rizzo (1999)'s approach, by considering that detailing – and all the other promotion variables – investments in the previous 12 months (January 2011 to December 2011) were the same as in the period of January 2012 to December 2012. This approach has the advantage of simplicity, but has, according to Windmeijer et al (2006), a limitation, given the fact that typically the promotional investments tend to be higher in the initial periods of drug commercialization, and as a consequence the stock would be somewhat underestimated. But given the absence of real data from 12 months prior to the beginning of the dataset, this would be a possible solution to calculate the promotion stock
- The second is to follow Windmeijer et al (2006)'s approach, by estimating the promotion flow using the following model (figure 10.2):

$$promf_{iy} = \theta_{i0} + \theta_1 age_{iy} + v_{iy}$$

Figure 10.2 – Windmeijer et al (2006) promotion flow estimation

Source: Windmeijer et al (2006)

$Promf_{iy}$ represents the promotion expenditure for drug i in year y; age_{iy} is the age of the drug in years.

Compared to Rizzo (1999) and Windmeijer et al (2006)'s contributions, we are using much more promotion variables, which substantially increases the complexity of the model. We opted for using both approaches due to the following rationale.

In the cases where promotion variables investments did not evidence series continuity in the dataset, in the sense that investments appear apparently arbitrarily concentrated in a few months without a clear pattern, we follow Rizzo's approach. Most of the promotion tools using digital communication channels are included in this group, but also tools using traditional channels such as mailing, for some brands. Below is one example in figure 10.3, for digital (e-mailings) channels, for drug X (a drug selected from the database).

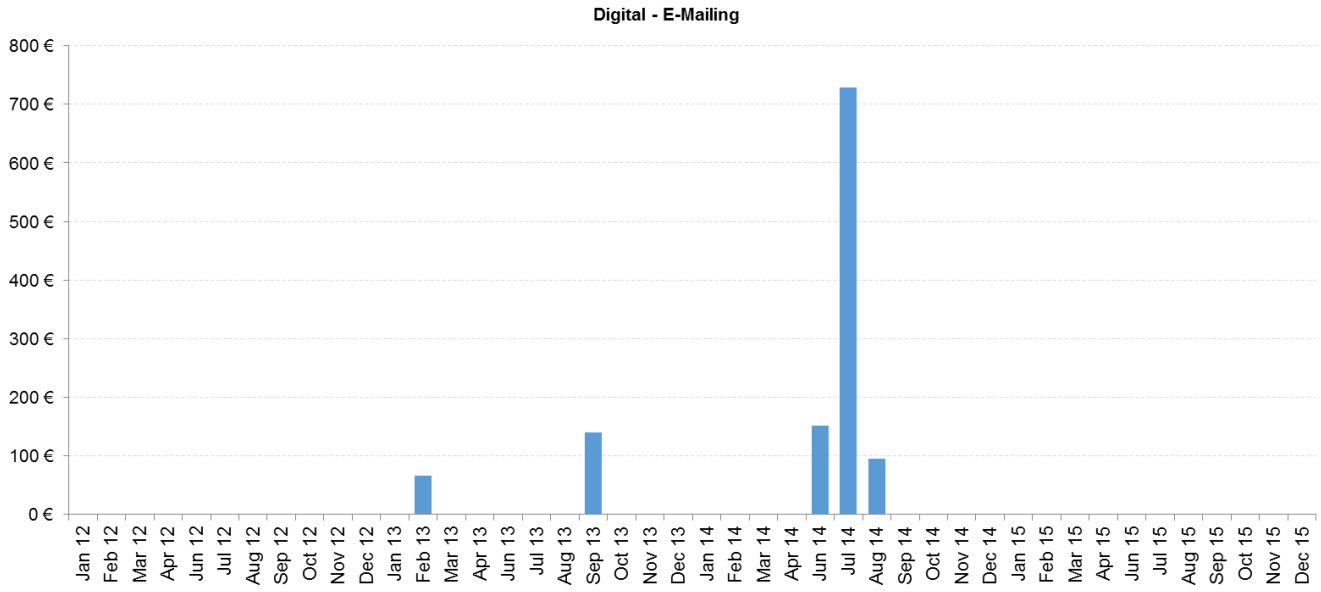


Figure 10.3 – Example of e-mailing investments for drug X

Source: own elaboration

In such cases, using Windmeijer et al (2006) promotion flow estimation for the previous periods based in time (drug age) might have produced unreliable flow estimates in these cases. Second, and related to the first, Windmeijer et al (2006)'s approach misses other independent variables than time itself, which are also not available in our dataset. In many cases, the products we analyzed had already been on the market for years prior to the initial observation provided by IQVIA, a situation similar to the one described by Rizzo (1999).

In the impossibility of going back in time and / or have access to additional information from IQVIA (which had no monthly data available before January 2012 for promotion investments), we assume, following Rizzo's approach, that the promotion investments in the prior 12 months were constant in real terms. This less complex approach, despite being discussable, appears to be reasonable in the perspective that the benefits of using a more parsimonious approach seem to be higher than the potential costs of using a smaller time series, and/or reaching unreliable estimates for most of the promotion tools in the dataset. To estimate the investment flows of the period of January 2011 to December 2011, we observed the following steps:

- First, we obtained the monthly consumer price indexes from the National Statistics Institute of Portugal. A screenshot of INE is shown in figure 10.4:

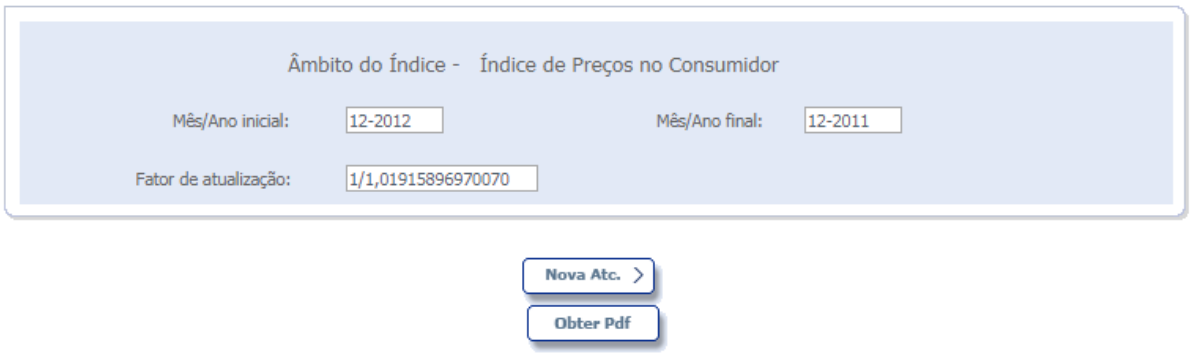


Figure 10.4 – INE Consumer price index

Source: INE (2018)

- Second, we calculated the discount factor, dividing 1 by the monthly price index
- Third, we estimated the promotion investments flow by multiplying the investments flow by the monthly discount factors. Steps two and three are illustrated in table 10.10, as an example for detailing.

Table 10.10 – Illustration of the calculation of own detailing stock

	Monthly consumer price index vs homologous period 2012	Monthly discount factor
January 2011	1,03525755741829	96,6%
February 2011	1,03608576346423	96,5%
March 2011	1,03159921946340	96,9%
April 2011	1,03016102098974	97,1%
May 2011	1,02706899191223	97,4%
June 2011	1,02717193558186	97,4%
July 2011	1,02778867045762	97,3%
August 2011	1,03088566323723	97,0%
September 2011	1,02884066092967	97,2%
October 2011	1,02130635030040	97,9%
November 2011	1,01885325258150	98,1%
December 2011	1,01915896970070	98,1%

	E-mailing flow 2012 for drug A	Estimated e-mailing flow 2011 for drug A
January	0	0
February	500	483
March	700	679
April	1000	971
May	0	0
June	0	0
July	0	0
August	0	0
September	200	194
October	0	0
November	0	0
December	0	0

Source: own elaboration

In the cases where promotion variables investments evidence series continuity (all or most of the months with data), we applied an adaptation of Windmeijer et al (2006) approach, by using a regression model with 13 independent variables. The dependent variable is promotion investments (from January 2012 to December 2015). The independent variables are 12 dummies for months, and one variable for time, for the same time period. We then computed

the expected investments backwards for the period of January 2011 to December 2011. Below we present an example computed for one of the drugs in the data series (here called product X), for face to face detailing (figure 10.5):

SUMÁRIO DOS RESULTADOS

Estatística de regressão	
R múltiplo	87,4%
Quadrado de R	76,5%
Quadrado de R a	65,6%
Erro-padrão	644,6755023
Observações	48

ANOVA

	gl	*SQ*	*MQ*	*F*	*ıle significância*
Regressão	13	47284357,3	3637258,26	9,48099483	7,3704E-08
Residual	35	14546227,6	415606,503		
Total	48	61830584,9			

	Coeficientes	*Erro-padrão*	*Stat t*	*valor P*	*95% inferior*	*95% superion*	*ferior 95,0%*	*uperior 95,0%*
Interceptar	422,3371875	387,463842	1,09000413	0,28315922	-364,25623	1208,9306	-364,2562	1208,9306
Time	66,7346875	6,93560412	9,62204392	2,3008E-11	52,6546626	80,8147124	52,654663	80,8147124
January	0	0	65535	#NUM!	0	0	0	0
February	-249,2346875	455,907177	-0,5466786	#NUM!	-1174,7755	676,306088	-1174,775	676,306088
March	749,905625	456,065414	1,644294	0,10906941	-175,95639	1675,76764	-175,9564	1675,76764
April	435,4209375	456,329021	0,954182	0,34653559	-490,97623	1361,8181	-490,9762	1361,8181
May	815,84875	456,697814	1,78640827	0,08269866	-111,2971	1742,9946	-111,2971	1742,9946
June	351,3015625	457,17154	0,76842395	0,44738948	-576,806	1279,40913	-576,806	1279,40913
July	128,216875	457,749872	0,28010248	0,78104778	-801,06477	1057,49852	-801,0648	1057,49852
August	-660,7803125	458,432415	-1,4413909	0,15836228	-1591,4476	269,886968	-1591,448	269,886968
September	39,91	459,218704	0,08690848	0,93123958	-892,35353	972,173532	-892,3535	972,173532
October	-78,3121875	460,108207	-0,1702038	0,86582989	-1012,3815	855,757132	-1012,382	855,757132
November	375,765625	461,100328	0,81493246	0,42062185	-560,31781	1311,84906	-560,3178	1311,84906
December	-650,1190625	462,194404	-1,4065922	0,16836588	-1588,4236	288,185461	-1588,424	288,185461

Figure 10.5 – Example of estimation of detailing flow – January 2011 to December 2011

The chart below (figure 10.6) presents the number of detailing visits for the period of January 2012 to December 2015 (lighter blue bars), and the estimated detailing investments for the period of January 2011 to December 2011 (darker blue bars).

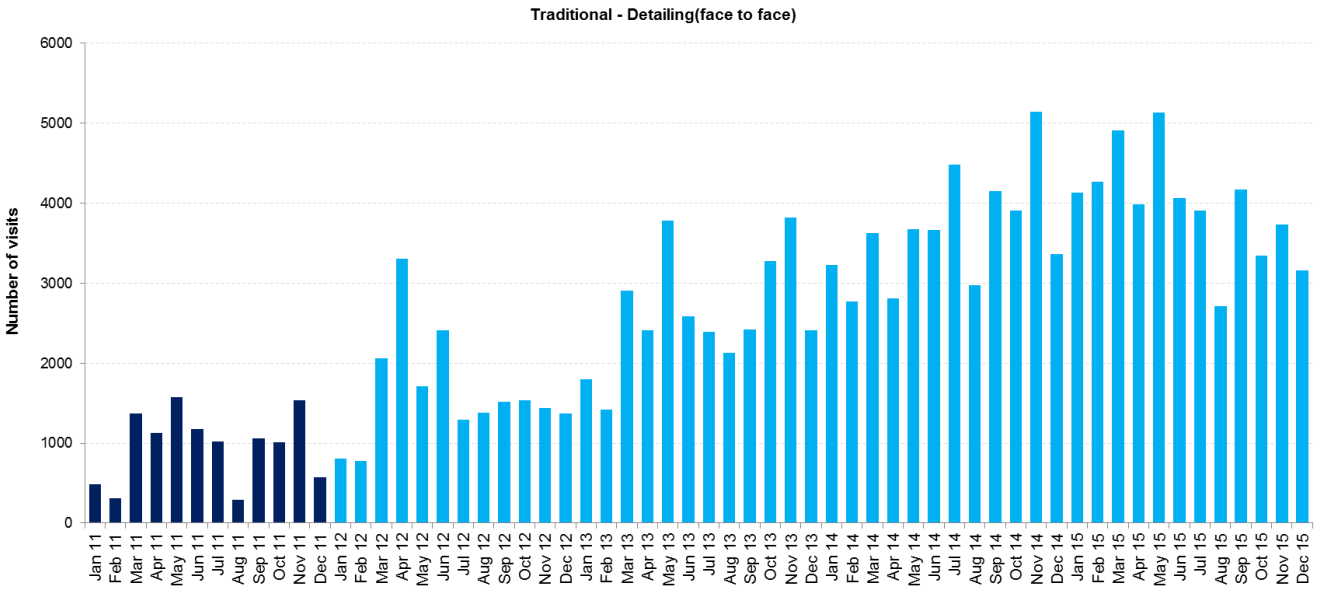


Figure 10.6 – Example of estimation of investments in the period of January 2011 to December 2011

Source: own elaboration

Negative estimated values were then manually converted into zeros (only a limited number of cases).

In both approaches, as we get closer to January 2013, promotional investments stock will be progressively more reliable, since we are using more observations from which we had real investments (for instance, the detailing stock in July 2012 will have six observations from the year 2012, using a very conservative carryover discount factor (30%). Table 10.11 below lists the methods applied for each of the applicable variables.

Table 10.11 – Methods used for estimation of past promotion investments (year of 2011)

		Method applied for 2011 investments estimation		
Market	**Product**	**Detailing flow (calls and €; own)**	**Other marketing expenditures flow (own)**	**Competitive global marketing expenditures flow**
Market 1 - Blood	**BL1**	Regression	Regression	Regression
	BL2	Regression	Regression	Regression
	BL3	N/A (consistent promotion activities started in 2014)		Regression
Market 2 - Pancreas	**PA1**	Regression	Regression	Regression
	PA2	Regression	Regression	Regression
	PA3	Regression	Regression	Regression
	PA4	N/A (consistent detailing activities started in 2013)	Rizzo (1999)	Regression
	PA5	Regression	Regression	Regression
Market 3 - Heart	**HE1**	Regression	Rizzo (1999)	Regression
	HE2	Regression	Regression	Regression
	HE3	Regression	Rizzo (1999)	Regression
	HE4	Rizzo (1999)	N/A (no other marketing expenditures in 2012 and 2013)	Regression
	HE5	N/A (consistent promotion activities started in 2013)		Regression
Market 4 - Liver	**LI1**	Regression	Rizzo (1999)	Regression
	LI2	Regression	Rizzo (1999)	Regression
	LI3	Regression	Rizzo (1999)	Regression
	LI4	Regression	Rizzo (1999)	Regression
	LI5	Rizzo (1999)	Rizzo (1999)	Regression

Source: own elaboration

10.1.4.6. Drug age

Drug age in months was calculated using IQVIA's variable "Commercialization launch date", which consists of the date (month / year) when the drug was launched in the market, in Portugal. If for instance a drug was commercially launched in January 2012, then a numeric sequence would start with number 1 for January 2011, 2 for February 2012, and so on. Then we created another variable called Drug age squared (Drug age^2), following Leeflang &

Wieringa (2010)'s approach. Table 10.12 below illustrates an example of drug age calculation.

Table 10.12 – Illustration of the calculation of drug age

		Drug age in months	Drug age in months squared
Launch date →	January 2012	1	1
	February 2012	2	4
	March 2012	3	9
	April 2012	4	16
	May 2012	5	25
	June 2012	6	36
	July 2012	7	49
	August 2012	8	64
	September 2012	9	81
	October 2012	10	100
	November 2012	11	121
	December 2012	12	144
	…	…	…
	November 2015	47	2209
	December 2015	48	2304

Source: own elaboration

In cases where more than one presentation of the same product was being commercialized (ex: 10mg pills, 20mg pills, and so on), the commercialization launch date was set at the date where the first presentation was available in the market. Table 10.13 below exhibits an illustrative example.

Table 10.13 – Example of multiple launch dates for the same product

	Presentation	Commercialization launch date
Product X	Presentation 1	2012/Mar
	Presentation 2	2012/Apr
	Presentation 3	2008/Dec
	Presentation 4	2008/Dec
	Presentation 5	2012/Apr
	Presentation 6	2012/Apr

Source: own elaboration

Therefore, for this product, the commercial launch date was set at December 2008.

10.1.4.7. Other promotion variables

In the case of the three variables shaded with a darker background in Table 10.5 – Promotion variables description -, we considered the options with the declared stronger impact which are: «Very useful and of value to your practice», «Frequently», and «Increase / will begin to prescribe». These independent variables percentages were calculated using a weighted average considering the number of calls in each of the rows of the database, for each of the products in our analysis. Regarding the number of products presented during the sales call, we updated the answers «>3» to 4 products, in order to have a numeric value. We believe this option will not impact robustness given two reasons: first, the percentage of «>3» answers is minimal (examples: average of 3,6% for product BL1, 1,8% for BL2, 1,6% for BL3); second, the literature has shown that a typical sales call includes up to three or four products, given its diminishing duration.

10.1.5. Promotion investments aggregation

As explained in topic 10.1.3. Variables description, we were given access to a substantially higher number of promotion tools expenditures than the ones used in previous research in the pharmaceutical marketing community. In order to test to maximize model comparison, we opted to aggregate the promotion investment expenditures so that we could use the same categories as Leeflang & Wieringa (2010). Therefore, we aggregated other promotion expenditures other than detailing, journal advertising, direct mail and meetings, using the following rationale (table 10.14).

Table 10.14 – Promotion aggregation investments

	Variables included
Other traditional marketing expenditures	Tele-detailing
	Samples
	Clinical trials
Digital marketing expenditures	E-mailing
	Virtual (self) e-detailing
	Video (live) e-detailing
	E-detailing (other)
	e-Meetings (automated)
	e-Meetings (live)
	Corporate website
Other traditional marketing expenditures	All promotion variables except detailing

Source: own elaboration

10.1.5.1. Available independent variables

Based on the provided variables, we prepared a database to allow maximum possibilities of applying previously developed models, and also allow the usage of new variables (to the best of our knowledge, this is the first research using the variables shaded in a darker blue in table 10.15).

Table 10.15 – Final list of variables included for potential analysis

		Logarithmized?	Variable name in SPSS	Variable description in SPSS
Current period sales (dependent)		Yes	sales_ddd	Ln Sales in DDDs
Lagged sales in DDDs		Yes	sales_ddd_lag1	Ln Sales in DDDs lagged one period
		Yes	sales_ddd_lag2	Ln Sales in DDDs lagged two periods
Marketing expenditures flow	**Own**	Yes	det_calls	Ln Detailing flow (calls)
		Yes	det_calls_x_det_calls	Ln Detailing flow (calls) x Ln Detailing flow (calls)
		Yes	det_euro	Ln Detailing flow (€)
		Yes	det_euro_x_det_euro	Ln Detailing flow (€) x Ln Detailing flow (€)
		Yes	journal	Ln Journal advertising flow
		Yes	mailing	Ln Mailing flow
		Yes	meetings	Ln Meetings (live) flow
		Yes	other_trad	Ln Other traditional marketing expenditures flow
		Yes	digital	Ln Digital marketing expenditures flow
		Yes	ome	Ln Other marketing expenditures flow
		Yes	global_mkt_expend	Ln Global marketing expenditures flow
	Competitive	Yes	comp_det	Ln Competitive detailing flow (calls)
		Yes	comp_journal	Ln Competitive Journal advertising flow
		Yes	comp_mail	Ln Competitive mailing flow
		Yes	comp_meet	Ln Competitive meetings (live) flow
		Yes	compet_other_trad	Ln Competitive other traditional marketing expenditures flow
		Yes	compet_digit	Ln Competitive digital marketing expenditures flow
		Yes	compet_global	Ln Competitive global marketing expenditures flow
Marketing expenditures stock	**Own**	Yes	det_stock	Ln Detailing stock (calls)
		Yes	det_stock_x_det_stock	Ln Detailing stock (calls) x Ln Detailing stock (calls)
		Yes	ome_stock	Ln Other marketing expenditures stock
		Yes	glob_mkt_stock	Ln Global marketing expenditures stock
	Competitive	Yes	comp_mark_expend_stock	Ln Competitive global marketing expenditures stock
Drug price	**Own**	Yes	avg_price_ddd	Ln Average drug price per DDD
	Competitors	Yes	avg_comp_price_ddd	Ln Average competitors price per DDD
Drug age		No	drug_age	Drug age
		No	drug_age_sq	Drug age^2
		No	drug_age_cube	Drug age^3
Interactions		Yes	price_x_det	Ln Average drug price per DDD x Ln Detailing flow
		Yes	price_x_det_stock	Ln Average drug price per DDD x Ln Detailing stock
		Yes	price_x_age	Ln Average drug price per DDD x Drug age
		Yes	journal_x_det	Ln Journal advertising flow x Ln Detailing flow
		Yes	journal_x_mail	Ln Journal advertising flow x Ln Mailing flow
		Yes	mail_x_det	Ln Mailing flow x Ln Detailing flow
		Yes	global_mkt_stock_x_drug_price	Ln Global marketing expenditures stock x Ln Average drug price per DDD
		Yes	global_mkt_stock_x_comp_price	Ln Global marketing expenditures stock x Ln Average competitors price per DDD
Policy change dummies		No	reimbursem	Public reimbursement (dummy)
		No	loss_exclusivity	Loss of exclusivity (dummy)
		No	det_ceiling	Detailing ceiling entry into force (dummy)
		No	electronic_rx	Compulsory electronic prescription (dummy)
Year and month dummies		No	y2013 to y2015	Year 2013 (dummy) to Year 2015 (dummy)
		No	m2 to m12	Month 2 (dummy) to Month 12 (dummy)
Visual Aid Type		No	ipad_tablet	Ipad / Tablet (% of times used in calls)
		No	laptop	Laptop based materials (% of times used in calls)
		No	printed	Printed material (% of times used in calls)
Interest of the contact		No	very_useful	Very useful (% of calls)
Prescription - future (intention)		No	incr_or_begin	Increase / Will begin to prescribe (% of calls)
Number of products presented		Yes	nr_products	Ln Avg number of products presented during the calls

Source: own elaboration

In some of the variables where no variation was present (that is, the variable had the same values for the whole time series), we opted to remove them from the respective model, following Leeflang, Wieringa, Bijmolt & Pauwels (2015)'s approach («*If price (or another variable for that matter) is relatively stable over the period of observation, then it cannot have much explanatory power in the sample*» (p. 244).

10.2. Expected signals of the coefficients

We proceeded to a theory analysis of the expected signals of the coefficients of all variables used by authors addressed by Leeflang & Wieringa (2010), summarizing the gathered information on table 10.16 below.

Table 10.16 – Expected signals of coefficients

				Expected signal	Theoretical grounding (non-exhaustive)
Independent variables	Lagged sales		Ln Lagged sales period t-1	Positive	Windmeijer et al (2006) | Leeflang & Wieringa (2010)
			Ln Lagged sales period t-2	Positive	Windmeijer et al (2006) | Leeflang & Wieringa (2010)
	Marketing expenditures flow	Own	Ln Detailing flow	Positive	Kremer et al (2008) | Stremersch & Van Dyck (2009)
			Ln Detailing flow x Ln Detailing flow	Negative	Gönül et al (2001) | Manchanda & Chintagunta (2004)
			Ln Journal advertising flow	Positive	Pitt & Nel (1988) | Williams & Hensel (1991)
			Ln Direct marketing flow	Positive	Parsons & Abeele (1981) | Williams & Hensel (1991)
			Ln Marketing expenditures flow	Positive	Leeflang & Wieringa (2010)
		Competitive	Ln Competitive detailing flow	Negative	Leeflang & Wieringa (2010)
			Ln Competitive journal advertising flow	Negative	Leeflang & Wieringa (2010)
			Ln Competitive direct marketing flow	Negative	Leeflang & Wieringa (2010)
			Ln Competitive marketing expenditures flow	Negative	Leeflang & Wieringa (2010)
	Marketing expenditures stock	Own	Ln Detailing stock	Positive	Narayanan et al (2004) | Leeflang & Wieringa (2010)
			Ln Detailing stock x Ln Detailing stock	Positive	Rizzo (1999)
			Ln Marketing expenditures stock	Positive	Inferred from Leeflang & Wieringa (2010)
		Competitive	Ln Competitive global marketing expenditures stock	Negative	Leeflang & Wieringa (2010)
	Price	Own	Ln Average drug price per DDD	Negative	Leeflang & Wieringa (2010)
		Competitors	Ln Average competitors drug price per DDD	Positive	Leeflang & Wieringa (2010)
	Drug age		Drug age	Positive	Wittink (2002) | Leeflang & Wieringa (2010)
			Drug age x Drug age	Negative	Wittink (2002) | Leeflang & Wieringa (2010)
			Drug age x Drug age x Drug age	---	Not explicitly shown in Wittink (2002)
	Marketing expenditures interactions		Average drug price per DDD x Ln Detailing flow	Positive	Rizzo (1999) | Leeflang & Wieringa (2010)
			Ln Average drug price per DDD x Ln Detailing stock	Positive	Rizzo (1999) | Leeflang & Wieringa (2010)
			Ln Average drug price per DDD x Drug age	Negative	Rizzo (1999)
			Ln Journal advertising flow x Ln Detailing flow	---	Not explicitly shown in Wittink (2002)
			Ln Journal advertising flow x Ln Mailing flow	---	
			Ln Mailing flow x Ln Detailing flow	---	
			Ln Global marketing expenditures stock x Ln Average drug price per DDD	Positive	Windmeijer et al (2006) | Leeflang & Wieringa (2010)
			Ln Global marketing expenditures stock x Ln Average competitors price per DDD	Negative	Windmeijer et al (2006) | Leeflang & Wieringa (2010)
	Policy change dummies		Detailing ceiling (restriction policy)	Negative	Liu, Gupta, Venkataraman & Liu (2016) | Larkin et al (2017)
			Drug public reimbursement	Positive	Scherer (1993)
			Loss of exclusivity	Negative	Aitken et al (2013)

Source: own elaboration

10.3. Descriptive analysis

This sub-chapter will briefly describe each of the products selected for analysis, in terms of sales, detailing, and global promotion expenditures evolution. Specific issues such as policy changes will be highlighted (ex: start of public reimbursement).

10.3.1. Market 1 - Blood

Market 1 comprises a subset of a larger market that treats blood-related health issues, and includes, in a specific type of treatments, three competitors. These competitors are very expensive drugs, comparing their price against the traditional therapies used before the appearance of this new class of treatments. Table 10.17 provides a general characterization of each of the selected products in Market 1.

Table 10.17 – Products characterization in Market 1 – Blood

				In the period of January 2012 to December 2015…				
	Criterion	**Brand**	**Number of main competitors**	**Was commercialization initiated?**	**Loss exclusivity?**	**Suffered from generics competition (same molecule)?**	**Was promoted in co-marketing?**	**If promoted in co-marketing, with which brand?**
Market 1 - Blood	**Rank 1 in sales** (sell-in, ∑2012-2015)	BL1	2	No	No	No	No	N/A
	Rank 2 in sales (sell-in, ∑2012-2015)	BL2	2	No	No	No	No	N/A
	One that entered the market (2012-2015)	BL3	2	Yes (Jul 2014)	No	No	No	N/A

Source: own elaboration

Figure 10.7 below explores additional insights regarding Market 1. Product BL2 was the first one of this class to be launched, representing a significant burden to the NHS. Product BL1 followed (received public reimbursement in August 2014, moment after which sales grew substantially. Product BL3 was the third entering this new class, investing heavily in detailing and in meetings (live).

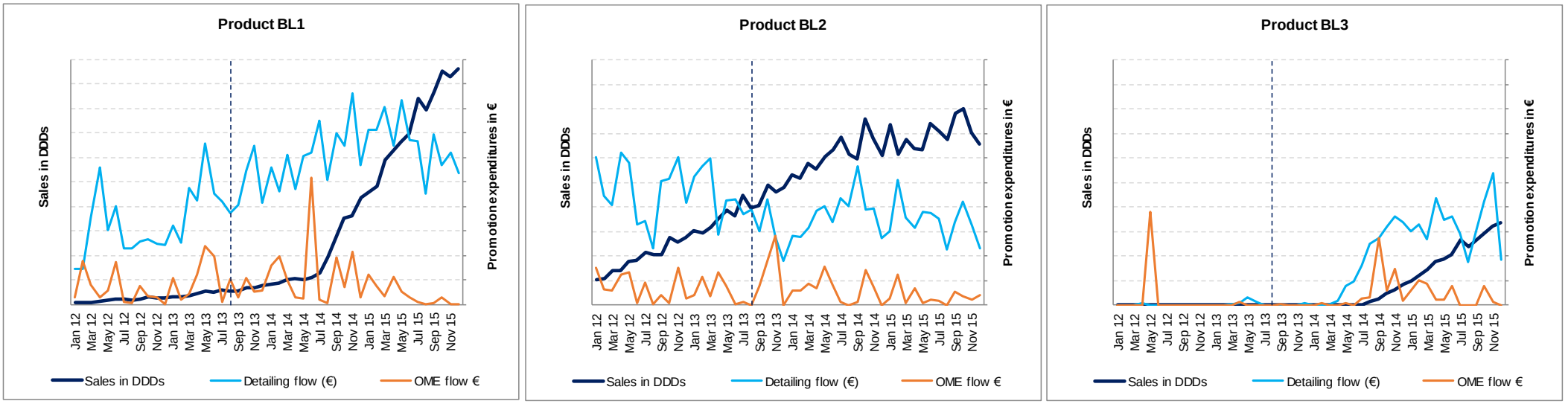


Figure 10.7 – Sales in DDDs, and detailing and other marketing expenditures (OME) flow for Products BL1, BL2 and BL3

Source: own elaboration

Please note:

- Two vertical axis were set: the one on the left represents Sales in DDDs, and the one on the right represent marketing expenditures in Euros (detailing flow and OME)

- In Market 1, as well as in all other three markets, both vertical axis were forced to a fixed scale, in order to allow a better visual perception of the relative magnitude of both sales and marketing expenditures across all the products in each market
- The vertical dashed line represents the entry into force of the detailing restriction policy (detailing ceiling), on August 2013

Figure 10.8 below represents the boxplots of sales in DDDs, number of calls, and OME for each of the three products of Market 1. It provides additional description, complementary to the time series approach followed by providing the charts presented above.

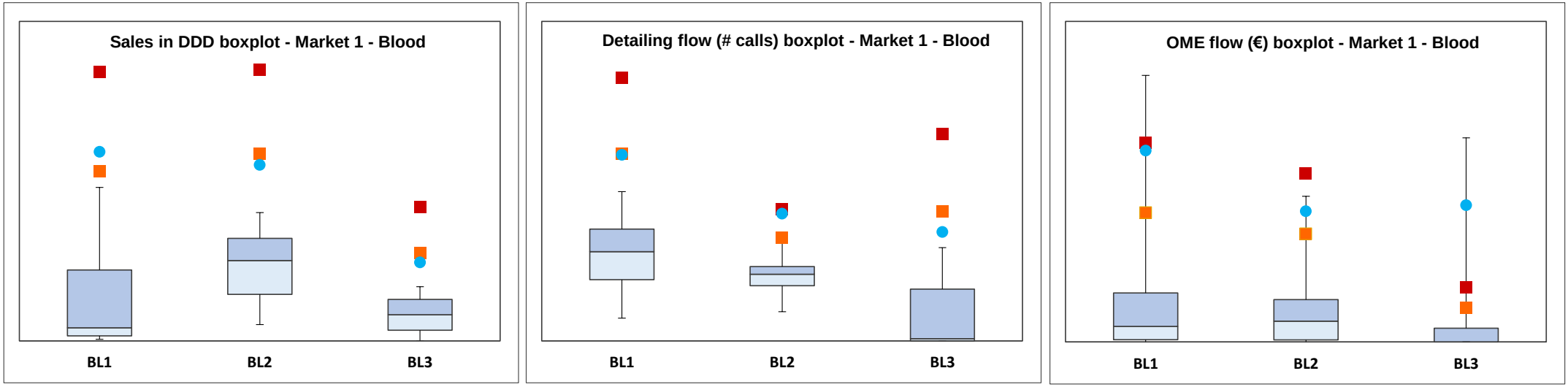


Figure 10.8 – Market 1 boxplots (sales in DDDs, number of calls, and OME)

Source: own elaboration

Interestingly, product BL1 has a very long “whisker” represented by the difference between the maximum and quartile 3, explained by the rapid acceleration of sales in the last observations of the time series (this can be seen in the previously presented chart, in figure 10.7). The lower “whisker” is represented by the difference between quartile 1 and the minimum. The first line in each box represents quartile 1, the second line represents the median, and the third line represents quartile 3. The dark blue shade therefore represents the difference between quartile 3 and the median, and the light blue shade represents the difference between the median and quartile 1. In order to search for outliers, we proceeded to the following calculations:

- Left inner fence = Q1 – 1,5 x IQR (quartile 1 minus 1,5 x interquartile range)
- Left outer fence = Q1 – 3,0 x IQR
- Mean minus 3 stdv = $\overline{x} - 3\sigma$
- Right inner fence = Q3 + 1,5 x IQR, represented by an orange shaded square
- Right outer fence = Q3 + 3,0 x IQR, represented by a red shaded square
- Mean plus 3 stdv = $\overline{x} + 3\sigma$, represented by a blue shaded circle

In order to summarize results in order to averiguate the existence of outliers, we built table 10.18.

Table 10.18 – Summary of the boxplots results – Market 1 (Blood)

		Sales in DDDs			Detailing flow (calls)			OME flow (€)		
		BL1	BL2	BL3	BL1	BL2	BL3	BL1	BL2	BL3
Is maximum…	Higher than right outer fence?	No	No	No	No	No	No	Yes	No	Yes
	Higher than right inner fence?	No	No	No	No	Yes	No	Yes	Yes	Yes
	Higher than $\bar{x}$ + 3σ?	No	No	No	No	No	No	Yes	Yes	Yes

		Sales in DDDs			Detailing flow (calls)			OME flow (€)		
		BL1	BL2	BL3	BL1	BL2	BL3	BL1	BL2	BL3
Is minimum…	Lower than left outer fence?	No	No	No	No	No	No	No	No	No
	Lower than left inner fence?	No	No	No	No	No	No	No	No	No
	Lower than $\bar{x}$ - 3σ?	No	No	No	No	No	No	No	No	No

Source: own elaboration

We concentrate our attention on the situations where the maximum is higher than the right outer fence (first row of the table). In this market, the apparent outliers are all explained by marketing decisions regarding the intensity of promotion investments. For instance, product BL1 evidenced a huge increment in face-to-face meetings two months before the approval of its public reimbursement. Product BL3 registered higher promotion expenditures in face-to-face meetings too, associated with planned initiatives.

As a conclusion of this analysis, we did not proceed to any outlier treatment, given that the ones detected were explained by the marketing activities of the pharmaceutical companies. Therefore, data modelling used the full time series of data.

10.3.2. Market 2 - Pancreas

Market 2 comprises five products that treat a health issue provoked by a pancreas non-optimal functioning. It includes five products, four of which promoted in co-marketing (same active principle, but a different commercial brand). One of the products started its commercialization four months before the entry into force of the detailing ceiling. Table 10.19 provides general characterization of the products selected for analysis in this market.

Table 10.19 – Products characterization in Market 2 – Pancreas

				In the period of January 2012 to December 2015…				
	Criterion	**Brand**	**Number of main competitors**	**Was commercialization initiated?**	**Lost exclusivity?**	**Suffered from generics competition (same molecule)?**	**Was promoted in co-marketing?**	**If promoted in co-marketing, with which brand?**
Market 2 - Pancreas	**Rank 1 in sales** (sell-in, ∑2012-2015)	PA1	5	No	No	No	Yes	2 brands not in the brand selection
	Rank 2 in sales (sell-in, ∑2012-2015)	PA2	5	No	No	No	Yes	PA3 and PA5
	Rank 3 in sales (sell-in, ∑2012-2015)	PA3	5	No	No	No	Yes	PA2 and PA5
	One that entered the market (2012-2015)	PA4	5	Yes (Apr 2013)	No	No	No	N/A
	Another one of interest	PA5	5	No	No	No	Yes	PA2 and PA3

Source: own elaboration

The behavior in terms of the evolution of sales in DDDs, detailing flow and other marketing expenditures is shown below in figure 10.9. Products PA1 and PA2 are the market leaders. Product PA4 evidenced a very substantial investment in detailing activities right before the product commercial launch.

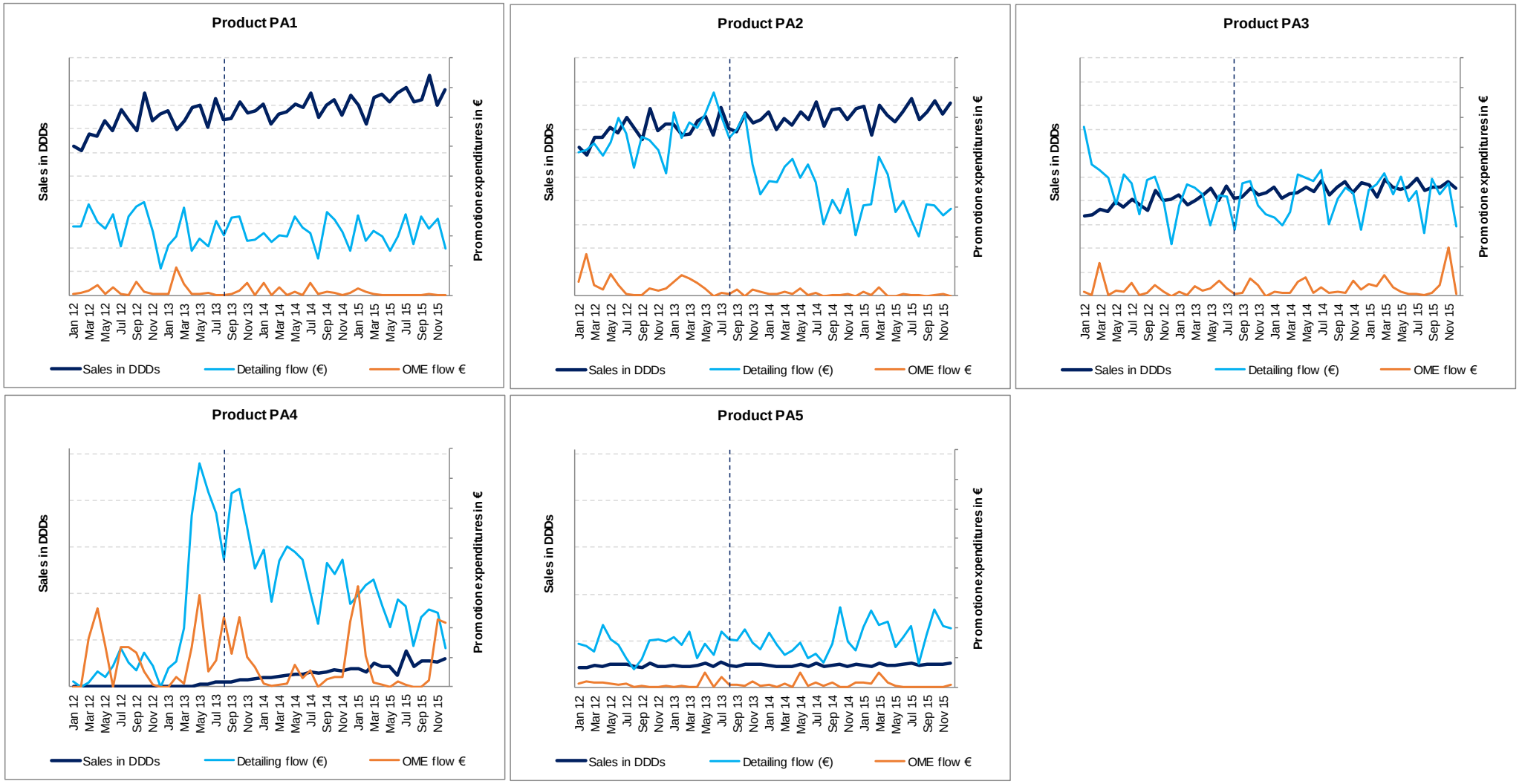


Figure 10.9 – Sales in DDDs, and detailing and other marketing expenditures (OME) flow for Products PA1, PA2, PA3, PA4 and PA5

Source: own elaboration

The boxplots regarding market 2 are shown below, in figure 10.10.

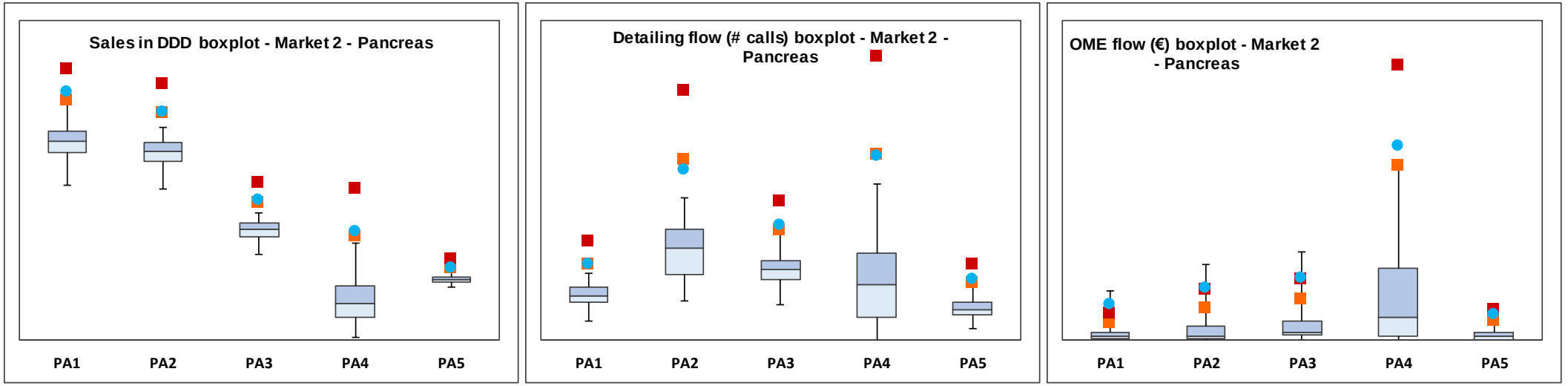


Figure 10.10 – Market 2 boxplots (sales in DDDs, number of calls, and OME)

Source: own elaboration

Based on the interpretation of the sales in DDDs boxplots, we can confirm the insights gathered by interpreting the time series chart: these products (except product PA4) are mature products, with very little variation in their time series. Product PA4 was the one with the higher investments in other marketing expenditures (OME), in the period of analysis, mainly explained by big investments in clinical trials.

Just as performed regarding market 1, we searched for the existence of outliers, which data is summarized below in table 10.20:

Table 10.20 – Summary of the boxplots results – Market 2 (Pancreas)

		Sales in DDDs					Detailing flow (calls)					OME flow (€)				
		PA1	PA2	PA3	PA4	PA5	PA1	PA2	PA3	PA4	PA5	PA1	PA2	PA3	PA4	PA5
Is maximum …	Higher than right outer fence?	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
	Higher than right inner fence?	No	No	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
	Higher than $\bar{x} + 3\sigma$?	No	No	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No	Yes

		Sales in DDDs					Detailing flow (calls)					OME flow (€)				
		PA1	PA2	PA3	PA4	PA5	PA1	PA2	PA3	PA4	PA5	PA1	PA2	PA3	PA4	PA5
Is minimum …	Lower than left outer fence?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
	Lower than left inner fence?	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No
	Lower than $\bar{x} - 3\sigma$?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

Source: own elaboration

Again, we concentrate our focus on the first row. Products PA1, PA2 and PA3 apparently have outliers in OME. A closer analysis reveals that product PA1 substantially increased its face-to-face meetings expenditures two months before product PA4 start of commercialization. Products PA2 and PA3 are promoted in co-marketing with product PA5, and the peak in OME was justified by higher than average investments in face-to-face meetings too, in the scope of the regular promotion strategy. Therefore, we accepted all observations and used all data points in the data modelling phase.

10.3.3. Market 3 - Heart

Market 3 handles a heart-related pathology affecting a subtantial proportion of the Portuguese population. Four of the brands are co-marketed.

General characterization of the selected products in Market 3 is shown below in table 10.21.

Table 10.21 – Products characterization in Market 3 – Heart

				In the period of January 2012 to December 2015…				
	Criterion	**Brand**	**Number of main competitors**	**Commercialization was initiated?**	**Lost exclusivity?**	**Suffered from generics competition (same molecule)?**	**Was promoted in co-marketing?**	**If promoted in co-marketing, with which brand?**
Market 3 - Heart	**Rank 1 in sales** (sell-in, ∑2012-2015)	HE1	5	No	No	No	Yes	1 brand not in the brand selection
	Rank 2 in sales (sell-in, ∑2012-2015)	HE2	5	No	No	No	Yes	1 brand not in the brand selection
	Rank 3 in sales (sell-in, ∑2012-2015)	HE3	5	No	Yes (Mar 2014)	Yes	Yes	1 brand not in the brand selection
	One that lost patent (2012-2015)	HE4	5	No	Yes (Sep 2012)	Yes	Yes	1 brand not in the brand selection
	One that entered the market (2012-2015)	HE5	5	Yes (Feb 2013)	No	No	No	N/A

Source: own elaboration

Figure 10.11 evidences the substantial sales loss of products HE3 and HE4. Product HE3, after having approaved a patent extension, lost its exclusivity in October 2013, but competitors only initiated their sales six months after, and therefore the dummy variable “Loss of exclusivity” will receive the value “1” from March 2014 to December 2015. Product HE4 lost its exclusivity in September 2012, and generics started their sales in that precise month. Both products evidenced residual detailing activity in the previous months before loss of exclusivity, comparing to the other products.

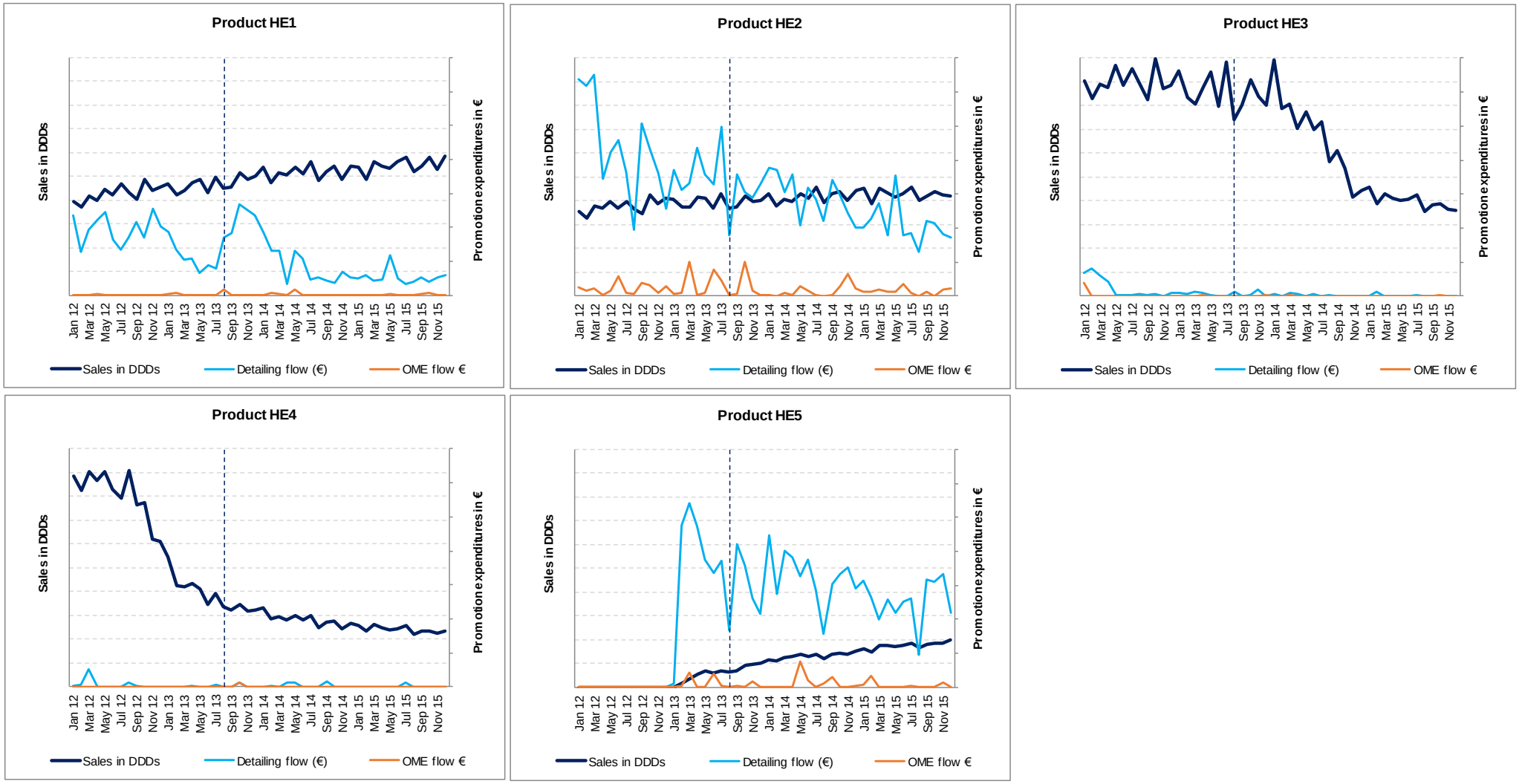


Figure 10.11 – Sales in DDDs, and detailing and other marketing expenditures (OME) flow for Products HE1, HE2, HE3, HE4 and HE5

Source: own elaboration

The boxplots regarding market 3 are shown below, in figure 10.12.

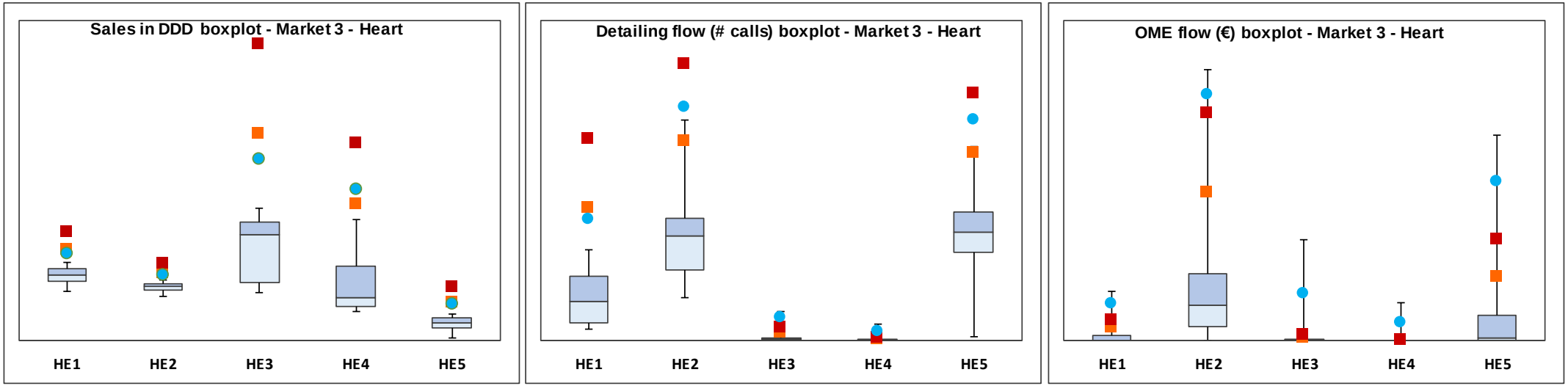


Figure 10.12 - Market 3 boxplots (sales in DDDs, number of calls, and OME)

Source: own elaboration

As seen above, products HE3 and HE4 lost their patent in 2012, and product HE5 was launched at the beginning of 2013. Products HE1 and HE2 are mature products, with very stabilized sales.

Table 10.22 below helped us identify potential outlier observations.

Table 10.22 – Summary of the boxplots results – Market 3 (Heart)

		Sales in DDDs					Detailing flow (calls)					OME flow (€)				
		HE1	HE2	HE3	HE4	HE5	HE1	HE2	HE3	HE4	HE5	HE1	HE2	HE3	HE4	HE5
Is maximum…	Higher than right outer fence?	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
	Higher than right inner fence?	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Higher than $\bar{x}$ + 3σ?	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

		Sales in DDDs					Detailing flow (calls)					OME flow (€)				
		HE1	HE2	HE3	HE4	HE5	HE1	HE2	HE3	HE4	HE5	HE1	HE2	HE3	HE4	HE5
Is minimum…	Lower than left outer fence?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
	Lower than left inner fence?	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No
	Lower than $\bar{x}$ - 3σ?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

Source: own elaboration

Concentrating our attention on the first row, we can see that there are several products with potential outliers in detailing flow and OME. In the case of detailing flow, products HE3 and HE4 substantially decreased their detailing expenditures, ending the period of analysis with zero calls. Therefore, given that this was a planned strategy after losing their patents (on March 2012 and September 2012, respectively), we will not eliminate any outlier observations. Regarding OME, we noticed that all five products appear to evidence strong outliers. We followed two approaches:

- Eliminated this variable in the case of product HE4 – this product had expenditures on OME in only one of the 48 months of the time series. Therefore, the regression model of product HE4 did not include this variable
- Did not eliminate any observation in the case of products HE1, HE2, HE3 and HE5, given that the investments in OME resulted from the normal business activity and planning. For example, product HE1 had a major mailing initiative in the summer of 2013, product HE2 launched a very strong face-to-face meeting initiave around the period when product HE5 was launched, product HE3 launched a face-to-face meetings initiative at the beginning of 2012 to resist the eminent loss of exclusivity, and product HE5 launched a face-to-face meetings initiative in the middle of quarter 2 2014 to help increase the slope of the sales growth (which had started to reduce its pace)

Products HE3 and HE4 were the only ones – in the markets and products perimeter selected for modelling - to incorporate the additional variable “Loss of exclusivity”, in the policy changes dummies.

10.3.4. Market 4 - Liver

Market 4 comprises five products that treat a health issue involving a non-optimal functioning of the liver. All five products are marketed in co-marketing, and are characterized in table 10.23 below.

Table 10.23 – Products characterization in Market 4 – Liver

				In the period of January 2012 to December 2015…				
	Criterion	**Brand**	**Number of main competitors**	**Commercialization was initiated?**	**Lost exclusivity?**	**Suffered from generics competition (same molecule)?**	**Was promoted in co-marketing?**	**If promoted in co-marketing, with which brand?**
Market 4 - Liver	**Rank 1 in sales** (sell-in, ∑2012-2015)	LI1	5	No	No	No	Yes	LI3
	Rank 2 in sales (sell-in, ∑2012-2015)	LI2	5	No	No	No	Yes	LI5
	Rank 3 in sales (sell-in, ∑2012-2015)	LI3	5	No	No	No	Yes	LI1
	One that entered the market (2012-2015)	LI4	5	No (started 7 montths before)	No	No	Yes	Another one not in the brand selection
	Another one of interest	LI5	5	No	No	No	Yes	LI2

Source: own elaboration

Product LI1 – co-marketed with product LI3 - is, by far, the leader in this market, but is not the strongest invester in detailing activities. Figure 10.13 below allows a better understanding of what happened in this market in terms of sales, detailing and OME for the five selected products.

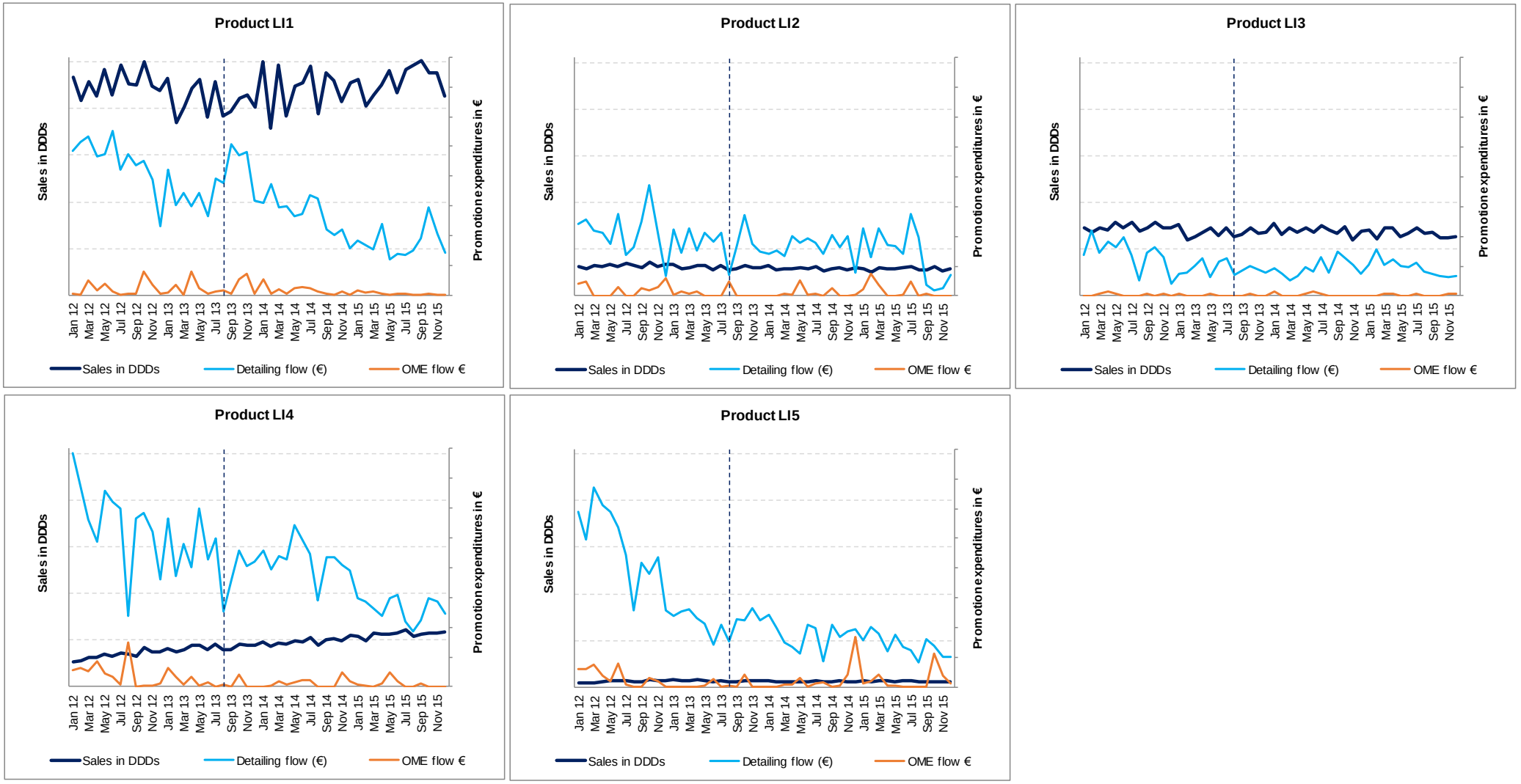


Figure 10.13 – Sales in DDDs, and detailing and other marketing expenditures (OME) flow for Products HE1, HE2, HE3, HE4 and HE5

Source: own elaboration

The boxplots regarding market 4 are shown below, in figure 10.14.

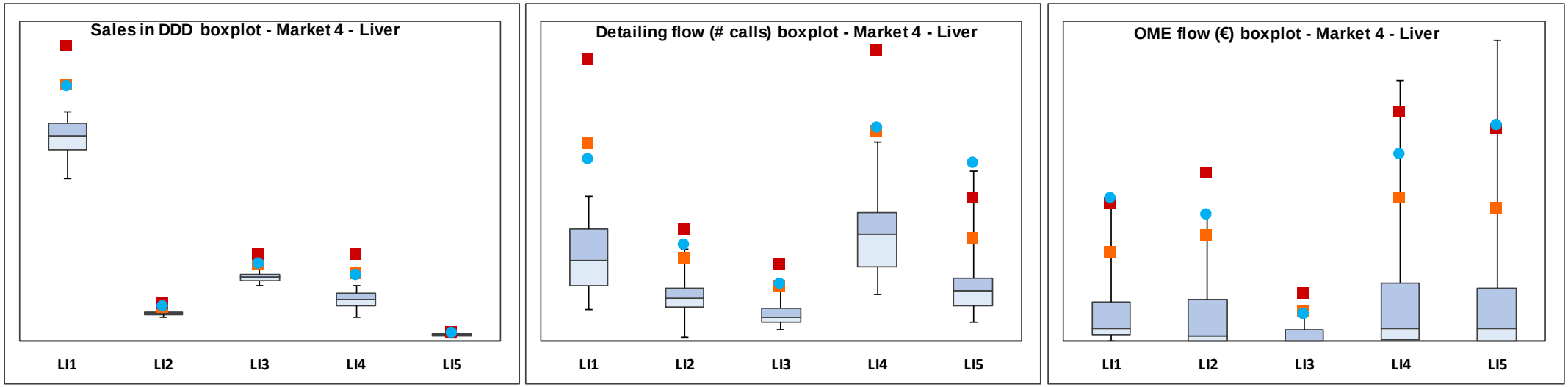


Figure 10.14 – Market 4 boxplots (sales in DDDs, number of calls, and OME)

Source: own elaboration

Market 4 products are also mature, with the exception of product LI4, launched in 2011. The OME boxplot evidences a great variation of the maximum montly investments among the five products. The high top whiskers of product LI4 in OME is mainly explained by higher investments in live meetings, while in product LI5 it is mainly explained by higher investments in face to face meetings and journal advertising.

Table 10.24 below helped us identify potential outlier observations.

Table 10.24 – Summary of the boxplots results – Market 4 (Liver)

		Sales in DDDs					Detailing flow (calls)					OME flow (€)				
		LI1	LI2	LI3	LI4	LI5	LI1	LI2	LI3	LI4	LI5	LI1	LI2	LI3	LI4	LI5
Is maximum…	Higher than right outer fence?	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	Yes	Yes
	Higher than right inner fence?	No	Yes	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
	Higher than $\bar{x}$ + 3σ?	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes

		Sales in DDDs					Detailing flow (calls)					OME flow (€)				
		LI1	LI2	LI3	LI4	LI5	LI1	LI2	LI3	LI4	LI5	LI1	LI2	LI3	LI4	LI5
Is minimum…	Lower than left outer fence?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
	Lower than left inner fence?	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No
	Lower than $\bar{x}$ - 3σ?	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No

Source: own elaboration

Concentrating our attention on the first row, we first analyzed product LI5 detailing flow. This product evidenced a higher than average number of calls during the first semester of 2012, with four very close values. We did not eliminate any observation for this reason (regular business operations and planning). We then looked at OME, starting with product LI1, which evidenced a strong investment in face-to-face meetings in a period where sales were starting to evidence some saturation in terms of growth rate. Product LI4 invested heavily in face-to-face meetings approximately after one year after product launch in order to re-ignite sales growth, and product LI5 invested substantially higher than average on face-to-face meetings at the end of 2014, in a moment where sales growth appeared to stagnate. Given these plausible reasons, we decided to keep all observations.

10.4. Application of four previous models

This chapter describes the data analysis performed with our data. We started by applying four different models, previously developed by Rizzo (1999), Wittink (2002), and Windemeijer et al (2006). We applied the models directly as they were used by their authors, to assess the extent to which they appear to fit to the Portuguese market reality. SPSS and Eviews complete set of outputs can be consulted at Appendix 6.

10.4.1. Necessary model adaptation

We have seen that all four models used in this chapter use temporal dummies (Rizzo 1999 used only year dummies, instead of year and month dummies). By applying the models directly using three dummies for the years (2013, 2014, and 2015) and 11 dummies for months (from February to December) we noticed some problems occurred: many variables were excluded by SPSS, situation which did not happen when the variable drug age in months was removed. There was therefore a mathematical problem, consisting of a perfect linear relationship between drug age in months and the year and month dummies. We exemplify with the output shown below (regarding product BL1, in figure 10.15):

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	1,000[a]	1,000	1,000	,000000000

a. Predictors: (Constant), Month 12 (dummy), Year 2015 (dummy), Month 11 (dummy), Month 10 (dummy), Month 9 (dummy), Month 8 (dummy), Month 7 (dummy), Month 5 (dummy), Year 2014 (dummy), Month 6 (dummy), Month 4 (dummy), Month 3 (dummy), Year 2013 (dummy), Month 2 (dummy)

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	9212,000	14	658,000	.	.[b]
	Residual	,000	33	,000		
	Total	9212,000	47			

a. Dependent Variable: Drug age

b. Predictors: (Constant), Month 12 (dummy), Year 2015 (dummy), Month 11 (dummy), Month 10 (dummy), Month 9 (dummy), Month 8 (dummy), Month 7 (dummy), Month 5 (dummy), Year 2014 (dummy), Month 6 (dummy), Month 4 (dummy), Month 3 (dummy), Year 2013 (dummy), Month 2 (dummy)

Coefficients[a]

Model		Unstandardized Coefficients B	Std. Error	t	Sig.
1	(Constant)	37,000	,000	.	.
	Month 2 (dummy)	1,000	,000	.	.
	Month 3 (dummy)	2,000	,000	.	.
	Month 4 (dummy)	3,000	,000	.	.
	Month 5 (dummy)	4,000	,000	.	.
	Month 6 (dummy)	5,000	,000	.	.
	Month 7 (dummy)	6,000	,000	.	.
	Month 8 (dummy)	7,000	,000	.	.
	Month 9 (dummy)	8,000	,000	.	.
	Month 10 (dummy)	9,000	,000	.	.
	Month 11 (dummy)	10,000	,000	.	.
	Month 12 (dummy)	11,000	,000	.	.
	Year 2013 (dummy)	12,000	,000	.	.
	Year 2014 (dummy)	24,000	,000	.	.
	Year 2015 (dummy)	36,000	,000	.	.

a. Dependent Variable: Drug age

Figure 10.15 – Regression of drug age in months on year and month dummies for product BL1

By using the coefficients shown in the table above, we computed the predicted drug age based on the real drug age (table 10.25). Naturally, we reached the exact real drug age, as shown below in regarding product BL1:

Table 10.25 – Demonstration of perfect linear relationship between drug age and year and month dummies

Drug Age (observed)	Y2013	Y2014	Y2015	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	Drug age (predicted)
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	37
38	0	0	0	1	0	0	0	0	0	0	0	0	0	0	38
39	0	0	0	0	1	0	0	0	0	0	0	0	0	0	39
40	0	0	0	0	0	1	0	0	0	0	0	0	0	0	40
41	0	0	0	0	0	0	1	0	0	0	0	0	0	0	41
42	0	0	0	0	0	0	0	1	0	0	0	0	0	0	42
43	0	0	0	0	0	0	0	0	1	0	0	0	0	0	43
44	0	0	0	0	0	0	0	0	0	1	0	0	0	0	44
45	0	0	0	0	0	0	0	0	0	0	1	0	0	0	45
46	0	0	0	0	0	0	0	0	0	0	0	1	0	0	46
47	0	0	0	0	0	0	0	0	0	0	0	0	1	0	47
48	0	0	0	0	0	0	0	0	0	0	0	0	0	1	48

In order to solve this mathematical problem, we replaced the monthly dummies by quarter dummies, therefore avoiding perfect collinearity. This option is consistent with the pharmaceutical industry practice, where the typical cycle is composed of three months. Table 10.26 below demonstrates how the month dummies were converted into quarter dummies.

Table 10.26 – Month to quarter dummies conversion

M4	M5	M6	M7	M8	M9	M10	M11	M12
Quarter 2			Quarter 3			Quarter 4		

Therefore, all models using monthly temporal dummies were adapted to incorporate quarter dummies instead.

10.4.2. Wittink (2002) simplified (Model 1)

10.4.2.1. Procedures and outputs

An adaptation of the model was made regarding product L14, which evidenced a very low variation in its price. One can see in figure 10.16 below that Ln average drug price for LI4 is almost a constant, with only a slight reduction of 0,5% in the drug price from January 2012 to December 2015. The decision to exclude this variable was based on its extremely high coefficient in the regression, with a price elasticity of -43,206, which manifestly appears to have very little relation with the reality in this market (descriptive statistics in figure 10.16).

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Ln Average drug price per DDD	48	-,662149	-,657012	-,65988440	,001260072
Valid N (listwise)	48				

Figure 10.16 – Descriptive statistics of variable Ln average drug price for product LI4

In order to allow a global view of the coefficients and significance, four tables – one for each market – were built, adapted from Leeflang & Wieringa (2010). Table 10.27 represents Market 1, table 10.28 represents Market 2, table 10.29 represents Market 3, and table 10.30 represents Market 4.

Table 10.27 – Summary of Wittink (2002) simplified (Model 1) regression outputs – Market 1 - Blood

Model specification			Wittink (2002) simplified											
			Product BL1				Product BL2				Product BL3			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			7,415	---	Yes	Yes	8,989	---	Yes	Yes	-26,503	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	-0,074	No	No	No	0,036	Yes	No	No	-0,192	No	Yes	Yes
		Ln Journal advertising flow	0,013	Yes	Yes	Yes	0,001	Yes	No	No	-0,027	No	Yes	Yes
		Ln Direct marketing flow	0,002	Yes	No	No	-0,001	No	No	No	0,018	Yes	No	Yes
	Competitive	Ln Competitive expend. flow	-0,009	Yes	No	No	0,060	No	No	No	0,418	No	Yes	Yes
Price	Own	Ln average drug price	-0,488	Yes	No	Yes	-0,805	Yes	No	Yes	1,712	No	No	No
Drug age		Drug age	0,100	Yes	Yes	Yes	0,111	Yes	Yes	Yes	1,246	Yes	Yes	Yes
		Drug age squared	-0,0003	Yes	No	Yes	-0,001	Yes	Yes	Yes	-0,014	Yes	Yes	Yes
Policy change (dummies)		Public reimbursement	0,491	Yes	Yes	Yes	-0,099	No	No	No	5,594	Yes	Yes	Yes
Temporal dummies		Quarter 2	0,113	---	No	No	0,056	---	No	No	-0,054	---	No	No
		Quarter 3	0,126	---	No	No	0,182	---	No	Yes	0,068	---	No	No
		Quarter 4	0,256	---	No	No	0,290	---	Yes	Yes	0,526	---	Yes	Yes
		Year 2013	0,157	---	No	No	0,266	---	No	No	N/A (product launched in 2014)			
		Year 2014	0,257	---	No	No	0,553	---	No	No				
		Year 2015	0,728	---	No	No	0,890	---	No	No	0,573	---	Yes	Yes
Adjusted R^2			0,995				0,982				0,999			
ANOVA Sig.			0,000				0,000				0,000			

Table 10.28 – Summary of Wittink (2002) simplified (Model 1) regression outputs – Market 2 – Pancreas

Model specification			Wittink (2002) simplified																	
			Product PA1				Product PA2				Product PA3				Product PA4				Product PA5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			13,402	---	Yes	Yes	14,720	---	Yes	Yes	11,243	---	Yes	Yes	1,972	---	No	No	13,275	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	-0,001	No	No	No	0,075	Yes	No	No	-0,072	No	No	Yes	-0,003	No	No	No	0,036	Yes	No	No
		Ln Journal advertising flow	0,00002	Yes	No	No	0,003	Yes	No	No	0,001	Yes	No	No	0,001	Yes	No	No	0,001	Yes	No	No
		Ln Direct marketing flow	-0,005	No	No	No	0,001	Yes	No	No	-0,002	No	No	No	0,033	Yes	No	No	-0,004	No	No	No
	Competitive	Ln Competitive expend. flow	0,046	No	No	No	0,010	No	No	No	0,140	No	Yes	Yes	0,400	No	No	Yes	0,048	No	No	No
Price	Own	Ln average drug price	0,434	No	No	No	-2,798	Yes	No	No	2,637	No	No	No	Constant (no variation)				-3,078	Yes	No	No
Drug age		Drug age	0,005	Yes	No	No	-0,010	No	No	No	0,006	Yes	No	No	0,282	Yes	Yes	Yes	-0,005	No	No	No
		Drug age squared	-0,0002	Yes	No	Yes	-0,0001	Yes	No	No	-0,0002	Yes	Yes	Yes	-0,003	Yes	Yes	Yes	#######	Yes	No	No
Temporal dummies		Quarter 2	0,125	---	Yes	Yes	0,069	---	No	Yes	0,111	---	Yes	Yes	-0,250	---	No	No	0,045	---	No	No
		Quarter 3	0,199	---	Yes	Yes	0,165	---	Yes	Yes	0,183	---	Yes	Yes	0,093	---	No	No	0,087	---	No	No
		Quarter 4	0,286	---	Yes	Yes	0,234	---	Yes	Yes	0,256	---	Yes	Yes	0,068	---	No	No	0,128	---	No	No
		Year 2013	0,250	---	Yes	Yes	0,184	---	No	No	0,264	---	Yes	Yes	N/A (product launched in 2013)				0,081	---	No	No
		Year 2014	0,507	---	Yes	Yes	0,352	---	No	No	0,629	---	Yes	Yes	0,059	---	No	No	0,045	---	No	No
		Year 2015	0,822	---	Yes	Yes	0,591	---	No	No	0,930	---	Yes	Yes	-0,123	---	No	No	0,176	---	No	No
Adjusted R^2			0,617				0,556				0,776				0,913				0,252			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,031			

Table 10.29 – Summary of Wittink (2002) simplified (Model 1) regression outputs – Market 3 – Heart

Model specification			Wittink (2002) simplified																	
			Product HE1				Product HE2				Product HE3				Product HE4				Product HE5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			14,735	---	Yes	Yes	14,560	---	Yes	Yes	10,504	---	No	No	39,118	---	Yes	Yes	6,263	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	0,023	Yes	No	No	0,062	Yes	Yes	Yes	0,006	Yes	No	No	0,012	Yes	No	No	-0,043	No	No	No
		Ln Journal advertising flow	-0,002	No	No	No	0,007	Yes	Yes	Yes	No investments in time series				No investments in time series				-0,006	No	No	No
		Ln Direct marketing flow	-0,011	No	Yes	Yes	-0,008	No	Yes	Yes	0,011	Yes	No	No	No investments in time series				0,010	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	0,013	No	No	No	-0,038	Yes	No	No	0,120	No	No	No	-0,090	Yes	No	No	0,277	No	No	No
Price	Own	Ln average drug price	0,981	No	No	No	-0,039	Yes	No	No	-0,290	Yes	No	No	-0,882	Yes	Yes	Yes	-0,746	Yes	No	No
Drug age		Drug age	0,012	Yes	No	No	0,004	Yes	No	No	0,065	No	No	No	-0,251	No	Yes	Yes	0,171	Yes	Yes	Yes
		Drug age squared	-0,0001	Yes	No	No	-0,0003	Yes	Yes	Yes	-0,0003	Yes	No	No	0,001	No	Yes	Yes	-0,002	Yes	Yes	Yes
Policy change (dummies)		Loss of exclusivity	Not applicable				Not applicable				-0,158	Yes	No	No	0,034	No	No	No	Not applicable			
Temporal dummies		Quarter 2	0,074	---	Yes	Yes	0,110	---	Yes	Yes	0,103	---	No	No	0,003	---	No	No	0,222	---	No	No
		Quarter 3	0,141	---	Yes	Yes	0,200	---	Yes	Yes	0,181	---	No	No	0,034	---	No	No	0,234	---	No	No
		Quarter 4	0,206	---	Yes	Yes	0,321	---	Yes	Yes	0,224	---	No	No	0,081	---	No	No	0,299	---	No	No
		Year 2013	0,207	---	No	Yes	0,336	---	Yes	Yes	0,261	---	No	No	-0,165	---	No	No	N/A (product launched in 2013)			
		Year 2014	0,481	---	Yes	Yes	0,740	---	Yes	Yes	0,607	---	No	No	-0,037	---	No	No	0,272	---	No	No
		Year 2015	0,753	---	Yes	Yes	1,202	---	Yes	Yes	0,748	---	No	No	0,079	---	No	No	0,651	---	No	No
Adjusted R^2			0,788				0,753				0,914				0,978				0,893			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,000			

Table 10.30 – Summary of Wittink (2002) simplified (Model 1) regression outputs – Market 4 – Liver

Model specification			Wittink (2002) simplified																	
			Product LI1				Product LI2				Product LI3				Product LI4				Product LI5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			17,824	---	Yes	Yes	17,955	---	Yes	Yes	12,972	---	Yes	Yes	12,705	---	Yes	Yes	7,190	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	-0,056	No	No	No	0,008	Yes	No	No	-0,008	No	No	No	0,081	Yes	No	No	0,063	Yes	No	No
		Ln Journal advertising flow	0,002	Yes	No	No	0,002	Yes	No	No	0,007	Yes	Yes	Yes	-0,0040	No	No	No	0,006	Yes	No	No
		Ln Direct marketing flow	-0,005	No	No	No	0,016	Yes	No	No	0,003	Yes	No	No	-0,006	No	No	No	-0,015	No	Yes	Yes
	Competitive	Ln Competitive marketing expenditures flow	0,118	No	No	No	-0,020	Yes	No	No	0,069	No	No	No	-0,012	Yes	No	No	-0,033	Yes	No	No
Price	Own	Ln average drug price	-0,962	Yes	No	No	-2,247	Yes	No	No	-0,965	Yes	No	No	Removed (almost constant)				4,782	No	Yes	Yes
Drug age		Drug age	-0,058	No	No	No	-0,036	No	No	No	0,011	Yes	No	No	0,012	Yes	No	No	0,033	Yes	No	Yes
		Drug age squared	0,0002	No	No	No	0,00001	No	No	No	-0,0001	Yes	No	No	-0,0003	Yes	Yes	Yes	-0,0006	Yes	Yes	Yes
Temporal dummies		Quarter 2	0,067	---	No	No	0,096	---	Yes	Yes	0,065	---	No	No	0,119	---	Yes	Yes	0,177	---	Yes	Yes
		Quarter 3	0,197	---	No	No	0,166	---	Yes	Yes	0,154	---	No	No	0,147	---	Yes	Yes	0,242	---	Yes	Yes
		Quarter 4	0,230	---	No	No	0,296	---	Yes	Yes	0,186	---	No	Yes	0,232	---	Yes	Yes	0,349	---	Yes	Yes
		Year 2013	0,244	---	No	No	0,313	---	Yes	Yes	0,141	---	No	No	0,233	---	No	Yes	0,566	---	Yes	Yes
		Year 2014	0,541	---	No	No	0,645	---	Yes	Yes	0,415	---	No	Yes	0,467	---	No	Yes	0,785	---	Yes	Yes
		Year 2015	0,819	---	No	No	1,003	---	Yes	Yes	0,672	---	No	Yes	0,846	---	Yes	Yes	1,367	---	Yes	Yes
Adjusted R^2			0,141				0,333				0,447				0,930				0,627			
ANOVA Sig.			0,135				0,008				0,001				0,000				0,000			

10.4.2.2. Results

Based on the four tables shown above, we prepared a summary of results for a better interpretation, with table 10.31.

Table 10.31 – Summary of Wittink (2002) simplified (Model 1) results

	Market 1 - Blood (3 products)				Market 2 - Pancreas (5 products)				Market 3 - Heart (5 products)				Market 4 - Liver (5 products)				Global (18 products)				Leeflang & Wieringa (2010) model application	
	% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities			
	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Signal as exp. and p<0.05	Obtained average elasticity (49 brands)
Ln Detailing flow	33,3%	0,0%	-0,077	0,036	40,0%	0,0%	0,007	0,056	80,0%	20,0%	0,012	0,026	60,0%	0,0%	0,018	0,051	55,6%	5,6%	-0,003	0,040	10,0%	0,014
Ln Journal advertising flow	66,7%	33,3%	-0,004	0,007	100,0%	0,0%	0,001	0,001	33,3%	33,3%	0,000	0,007	80,0%	20,0%	0,003	0,004	75,0%	18,8%	0,000	0,004	6,0%	0,027
Ln Direct marketing flow	66,7%	0,0%	0,006	0,010	40,0%	0,0%	0,005	0,017	50,0%	0,0%	0,000	0,010	40,0%	0,0%	-0,001	0,009	47,1%	0,0%	0,002	0,012	4,0%	0,007
Ln Competitive marketing expenditures flow	33,3%	0,0%	0,156	-0,009	0,0%	0,0%	0,129	N/A	40,0%	0,0%	0,056	-0,064	60,0%	0,0%	0,024	0,093	33,3%	0,0%	0,084	0,010	0,0%	0,053
Ln average drug price	66,7%	0,0%	0,140	-0,647	50,0%	0,0%	-0,701	-2,938	80,0%	20,0%	-0,195	-0,489	75,0%	0,0%	0,152	-1,391	68,8%	6,3%	-0,172	-1,209	---	---
Drug age	100,0%	100,0%	0,486	0,486	60,0%	20,0%	0,056	0,098	60,0%	20,0%	-0,251	0,063	60,0%	0,0%	-0,008	0,019	66,7%	27,8%	0,094	0,158	100,0%	0,170
Drug age squared	100,0%	66,7%	-0,005	-0,005	100,0%	40,0%	-0,001	-0,001	80,0%	40,0%	-0,001	-0,001	60,0%	40,0%	-0,0002	-0,0003	83,3%	44,4%	-0,001	-0,002	65,0%	-0,001
Public reimbursement	66,7%	66,7%	1,995	3,042	---	---	---	---	---	---	---	---	---	---	---	---	66,7%	66,7%	1,995	3,042	---	---
Loss of exclusivity	---	---	---	---	---	---	---	---	50,0%	0,0%	-0,062	-0,158	---	---	---	---	50,0%	0,0%	-0,062	-0,158	---	---

In this table, we added, in the last two columns, the results obtained by Leeflang & Wieringa (2010) using Model 1 with a 49 products in Dutch market, to serve as reference to the results obtained in our research using data from the Portuguese market.

10.4.3. Wittink (2002) complete (Model 2)

10.4.3.1. Procedures and outputs

We started running the first regressions and noted an issue with Model 2, where SPSS would exclude the variable Drug_age^2. To investigate this, we manually ran some regressions and found that, for the data set consisting of the temporal observations on our database, the variable Drug age^3 can be perfectly obtained from a linear combination of the variables Drug age and Drug age^2. Below we present the outputs of this regression for product BL1, in figure 10.17.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	1,000[a]	1,000	1,000	2151,976766

a. Predictors: (Constant), Drug age^2, Drug age

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1,228E+12	2	6,141E+11	132609,541	,000[b]
	Residual	208395180,0	45	4631004,000		
	Total	1,228E+12	47			

a. Dependent Variable: Drug age^3

b. Predictors: (Constant), Drug age^2, Drug age

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	200557,500	6432,385		31,179	,000
	Drug age	-10635,500	220,237	-,921	-48,291	,000
	Drug age^2	181,500	1,811	1,912	100,238	,000

a. Dependent Variable: Drug age^3

Figure 10.17 – Linear regression of Dru age^3 on Drug age and Drug age^2 for product BL1 in model 2

We also ran this regression for product BL2 (figure 10.18).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	1,000[a]	1,000	1,000	2151,976766

a. Predictors: (Constant), Drug age^2, Drug age

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1,013E+12	2	5,063E+11	109318,876	,000[b]
	Residual	208395180,0	45	4631004,000		
	Total	1,013E+12	47			

a. Dependent Variable: Drug age^3

b. Predictors: (Constant), Drug age^2, Drug age

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	170257,500	5792,899		29,391	,000
	Drug age	-9573,500	209,432	-,913	-45,712	,000
	Drug age^2	172,500	1,811	1,903	95,268	,000

a. Dependent Variable: Drug age^3

Figure 10.18 – Linear regression of Dru age^3 on Drug age and Drug age^2 for product BL1 in model 2

Therefore, to solve the multicollinearity provoked by the inclusion of Drug age^3, we decided to remove this variable from the list of variables in Model 2.

In addition to this global adaptation for all products, there was also the need to adjust Model 2 for some products. Regarding product BL3, we had to make a small adjustment corresponding to the complete version of Wittink (2002) explored by Leeflang & Wieringa (2010). SPSS excluded two variables in the regression in the case of product BL3, as seen in figure 10.19 below:

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Journal advertising flow	-,230[b]	-,093	,934	-,066	3,206E-5
	Drug age	3,772[b]	4,681	,043	,957	2,541E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Competitive mailing flow, Quarter 4 (dummy), Quarter 2 (dummy), Public reimbursement (dummy), Ln Competitive Journal advertising flow, Ln Journal advertising flow x Ln Detailing flow, Ln Detailing flow (calls), Ln Competitive detailing flow (calls), Quarter 3 (dummy), Ln Mailing flow, Ln Journal advertising flow x Ln Mailing flow, Drug age^2, Ln Mailing flow x Ln Detailing flow

Figure 10.19 – Rejected variables for product BL3 in model 2

We manually investigated the reason for the exclusion, and found that the variable Ln Journal advertising is dramatically correlated with Ln Journal advertising x Ln detailing flow, as seen below in figure 10.20:

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,999[a]	,998	,998	,214581746

a. Predictors: (Constant), Ln Journal advertising flow x Ln Detailing flow

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	327,646	1	327,646	7115,732	,000[b]
	Residual	,737	16	,046		
	Total	328,383	17			

a. Dependent Variable: Ln Journal advertising flow

b. Predictors: (Constant), Ln Journal advertising flow x Ln Detailing flow

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	,012	,071		,163	,872
	Ln Journal advertising flow x Ln Detailing flow	,134	,002	,999	84,355	,000

a. Dependent Variable: Ln Journal advertising flow

Figure 10.20 – Linear regression of Ln Journal advertising flow on its interaction with Ln detailing flow for product BL3 in model 2.

The fact that we are working with a limited number of observations for product BL3 (18 months only, given that it started its sales in July 2014), associated with the reality that a number of months has zero investments in journal advertising originated this almost perfect collinearity, rejected by SPSS. For visualization purposes, we show the observations for Ln Journal advertising flow and its interaction with Ln detailing flow, here seen in table 10.32.

Table 10.32 – Observations involved in variable rejection for product BL3 in model 2

	Ln Journal advertising flow	Ln Journal advertising flow x Ln Detailing flow
jul-14	8,5	58,8
ago-14	7,6	55,5
set-14	9,3	68,7
out-14	8,9	66,6
nov-14	8,8	67,5
dez-14	0,0	0,0
jan-15	8,8	65,7
fev-15	8,1	61,5
mar-15	8,1	60,4
abr-15	0,0	0,0
mai-15	0,0	0,0
jun-15	0,0	0,0
jul-15	0,0	0,0
ago-15	0,0	0,0
set-15	0,0	0,0
out-15	8,6	67,7
nov-15	0,0	0,0
dez-15	0,0	0,0

We then looked at variable Drug age, which was also rejected by SPSS. We ran some manual regressions and found that it is highly correlated with the dummy variable year 2015, as shown in figure 10.21.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,818[a]	,669	,648	3,167214865

a. Predictors: (Constant), Year 2015 (dummy)

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	324,000	1	324,000	32,299	,000[b]
	Residual	160,500	16	10,031		
	Total	484,500	17			

a. Dependent Variable: Drug age

b. Predictors: (Constant), Year 2015 (dummy)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	32,500	1,293		25,135	,000
	Year 2015 (dummy)	9,000	1,584	,818	5,683	,000

a. Dependent Variable: Drug age

Figure 10.21 – Linear regression of Drug age on Year 2015 dummy for product BL3 in model 2

It is demonstrated then that drug age is almost a linear perfect combination of the Year 2015 dummy. Again, the reduced number of observations and the fact that we are working with one-year dummy only (sales started in 2014) provoked this variable rejection.

In order to solve this problem, we decided to adapt model 2 for product BL3 by:

- Removing the interaction variable (Ln Journal advertising flow x Ln Detailing flow)
- Removing the year 2015 dummy

As a result, SPSS did not exclude any variable with this adapted model. Tables 10.33, 10.34, 10.35 and 10.36 show the results obtained in Model 2 for Markets 1, 2, 3 and 4.

Table 10.33 – Summary of Wittink (2002) compete (Model 2) regression outputs – Market 1 - Blood

Model specification			Wittink (2002) complete											
			Product BL1				Product BL2				Product BL3			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			3,511	---	No	Yes	8,003	---	Yes	Yes	-25,224	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	0,287	Yes	No	Yes	-0,017	No	No	No	-0,017	No	No	No
		Ln Journal advertising flow	0,279	Yes	No	Yes	0,086	Yes	No	No	-0,028	No	Yes	Yes
		Ln Direct marketing flow	0,135	Yes	No	No	-0,099	No	No	No	-0,274	No	No	No
	Competitive	Ln Competitive detailing flow	-0,050	Yes	No	No	0,033	No	No	No	-0,091	Yes	No	No
		Ln Competitive journal advertising flow	-0,004	Yes	No	No	0,012	No	Yes	Yes	-0,011	Yes	No	No
		Ln Competitive direct marketing flow	0,003	No	No	No	0,003	No	No	No	0,030	No	Yes	Yes
Drug age		Drug age	0,115	Yes	Yes	Yes	0,135	Yes	Yes	Yes	1,535	Yes	Yes	Yes
		Drug age squared	-0,0005	Yes	Yes	Yes	-0,001	Yes	Yes	Yes	-0,017	Yes	Yes	Yes
Interactions		Ln Journal advertising flow x Ln Detailing flow	-0,033	---	No	Yes	-0,012	---	No	No	---	---	---	---
		Ln Journal advertising flow x Ln Mailing flow	0,000	---	No	No	0,000	---	No	No	0,003	---	No	No
		Ln Mailing flow x Ln Detailing flow	-0,017	---	No	No	0,013	---	No	No	0,039	---	No	No
Policy change		Public reimbursement	0,631	Yes	Yes	Yes	-0,188	No	Yes	Yes	4,882	Yes	Yes	Yes
Temporal dummies		Quarter 2	0,178	---	Yes	Yes	0,081	---	No	No	-0,203	---	Yes	Yes
		Quarter 3	0,223	---	No	No	0,171	---	No	Yes	-0,077	---	No	No
		Quarter 4	0,328	---	No	No	0,261	---	No	Yes	0,251	---	No	Yes
		Year 2013	0,289	---	No	No	0,230	---	No	No	N/A (product launched in 2014)			
		Year 2014	0,428	---	No	No	0,411	---	No	No				
		Year 2015	1,008	---	No	No	0,688	---	No	No	---	---	---	---
Adjusted R^2			0,995				0,983				1,000			
ANOVA Sig.			0,000				0,000				0,000			

Table 10.34 – Summary of Wittink (2002) complete (Model 2) regression outputs – Market 2 – Pancreas

Model specification			Wittink (2002) complete																	
			Product PA1				Product PA2				Product PA3				Product PA4				Product PA5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			14,011	---	Yes	Yes	14,446	---	Yes	Yes	13,126	---	Yes	Yes	2,132	---	No	No	12,615	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	-0,029	No	No	No	0,076	Yes	No	No	-0,175	No	No	Yes	0,079	Yes	No	No	0,018	Yes	No	No
		Ln Journal advertising flow	-0,078	No	No	No	0,037	Yes	No	No	-0,040	No	No	Yes	-0,243	No	No	No	-0,019	No	No	No
		Ln Direct marketing flow	0,100	Yes	No	No	-0,097	No	No	No	-0,125	No	No	No	1,495	Yes	No	No	0,061	Yes	No	No
	Competitive	Ln Competitive detailing flow	0,054	No	No	No	-0,074	Yes	No	No	0,180	No	Yes	Yes	0,512	No	No	No	0,026	No	No	No
		Ln Competitive journal advertising flow	-0,004	Yes	No	No	0,003	No	No	No	0,004	No	No	No	0,0002	No	No	No	0,005	No	No	No
		Ln Competitive direct marketing flow	-0,004	Yes	No	No	-0,005	Yes	No	Yes	-0,003	Yes	No	No	0,032	No	No	No	-0,001	Yes	No	No
Drug age		Drug age	0,002	Yes	No	No	-0,005	No	No	No	0,004	Yes	No	No	0,272	Yes	No	No	0,002	Yes	No	No
		Drug age squared	-0,0002	Yes	No	Yes	-0,0001	Yes	No	No	-0,0002	Yes	No	Yes	-0,003	Yes	No	No	-0,0001	Yes	No	No
Interactions		Ln Journal advertising flow x Ln Detailing flow	0,010	---	No	No	-0,004	---	No	No	0,005	---	No	No	0,029	---	No	No	0,003	---	No	No
		Ln Journal advertising flow x Ln Mailing flow	0,002	---	No	Yes	0,000	---	No	No	-0,001	---	No	No	No interaction in time series				0,001	---	No	No
		Ln Mailing flow x Ln Detailing flow	-0,016	---	No	No	0,013	---	No	No	0,017	---	No	No	-0,200	---	No	No	-0,010	---	No	No
Temporal dummies		Quarter 2	0,109	---	Yes	Yes	0,076	---	Yes	Yes	0,098	---	Yes	Yes	-0,199	---	Yes	Yes	0,044	---	No	No
		Quarter 3	0,184	---	Yes	Yes	0,165	---	Yes	Yes	0,169	---	Yes	Yes	0,274	---	No	No	0,077	---	No	No
		Quarter 4	0,268	---	Yes	Yes	0,222	---	Yes	Yes	0,220	---	Yes	Yes	0,394	---	No	No	0,118	---	No	No
		Year 2013	0,262	---	No	Yes	0,175	---	No	No	0,223	---	No	Yes	N/A (product launched in 2013)				0,070	---	No	No
		Year 2014	0,505	---	No	Yes	0,407	---	No	Yes	0,464	---	Yes	Yes	0,565	---	No	No	0,107	---	No	No
		Year 2015	0,837	---	No	Yes	0,668	---	No	Yes	0,719	---	Yes	Yes	0,851	---	No	No	0,240	---	No	No
Adjusted R^2			0,621				0,551				0,765				0,845				0,171			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,136			

Table 10.35 – Summary of Wittink (2002) complete (Model 2) regression outputs – Market 3 – Heart

Model specification			Wittink (2002) complete																	
			Product HE1				Product HE2				Product HE3				Product HE4				Product HE5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			13,817	---	Yes	Yes	14,387	---	Yes	Yes	7,498	---	No	No	33,494	---	Yes	Yes	6,585	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	0,033	Yes	No	No	0,024	Yes	No	No	0,004	Yes	No	No	0,007	Yes	No	No	0,024	Yes	No	No
		Ln Journal advertising flow	0,074	Yes	No	No	-0,051	No	No	No	No investments in time series				No investments in time series				0,498	Yes	No	No
		Ln Direct marketing flow	-0,048	No	No	No	-0,082	No	No	No	0,009	Yes	No	No	No investments in time series				-0,711	No	No	No
	Competitive	Ln Competitive detailing flow	0,003	No	No	No	-0,022	Yes	No	No	0,122	No	No	No	-0,095	Yes	No	No	0,350	No	No	No
		Ln Competitive journal advertising flow	0,006	No	Yes	Yes	-0,002	Yes	No	No	0,002	No	No	No	0,009	No	Yes	Yes	-0,005	Yes	No	No
		Ln Competitive direct marketing flow	-0,0019	Yes	No	No	-0,001	Yes	No	No	-0,016	Yes	Yes	Yes	-0,004	Yes	No	No	0,013	No	No	No
Drug age		Drug age	0,020	Yes	No	No	0,009	Yes	No	No	0,122	Yes	No	Yes	-0,170	No	Yes	Yes	0,202	Yes	Yes	Yes
		Drug age squared	-0,0002	Yes	Yes	Yes	-0,0002	Yes	Yes	Yes	-0,001	Yes	Yes	Yes	0,0003	No	Yes	Yes	-0,002	Yes	Yes	Yes
Interactions		Ln Journal advertising flow x Ln Detailing flow	-0,011	---	No	No	0,007	---	No	No	No interactions in time series				No interactions in time series				-0,068	---	No	No
		Ln Journal advertising flow x Ln Mailing flow	No interactions in time series				0,002	---	Yes	Yes	No interactions in time series				No interactions in time series				0,002	---	No	No
		Ln Mailing flow x Ln Detailing flow	0,006	---	No	No	0,009	---	No	No	0,003	---	No	No	No interactions in time series				0,096	---	No	No
Policy change		Loss of exclusivity	Not applicable				Not applicable				-0,133	Yes	No	No	0,057	No	No	No	Not applicable			
Temporal dummies		Quarter 2	0,079	---	Yes	Yes	0,088	---	Yes	Yes	0,170	---	Yes	Yes	0,083	---	No	Yes	0,132	---	No	No
		Quarter 3	0,152	---	Yes	Yes	0,172	---	Yes	Yes	0,318	---	Yes	Yes	0,154	---	No	Yes	-0,043	---	No	No
		Quarter 4	0,219	---	Yes	Yes	0,263	---	Yes	Yes	0,409	---	Yes	Yes	0,206	---	No	Yes	-0,149	---	No	No
		Year 2013	0,229	---	No	Yes	0,265	---	Yes	Yes	0,434	---	No	Yes	-0,058	---	No	No	N/A (product launched in 2013)			
		Year 2014	0,565	---	Yes	Yes	0,609	---	Yes	Yes	0,929	---	No	Yes	0,243	---	No	No	-0,414	---	No	No
		Year 2015	0,898	---	Yes	Yes	1,030	---	Yes	Yes	1,408	---	No	Yes	0,575	---	No	No	-0,859	---	No	No
Adjusted R^2			0,823				0,693				0,924				0,979				0,869			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,000			

Table 10.36 – Summary of Wittink (2002) complete (Model 2) regression outputs – Market 4 – Liver

Model specification			Wittink (2002) complete																	
			Product LI1				Product LI2				Product LI3				Product LI4				Product LI5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			16,392	---	Yes	Yes	15,916	---	Yes	Yes	13,202	---	Yes	Yes	12,679	---	Yes	Yes	11,454	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	-0,118	No	No	Yes	0,005	Yes	No	No	-0,021	No	No	No	0,083	Yes	No	No	0,091	Yes	No	No
		Ln Journal advertising flow	-0,118	No	Yes	Yes	0,060	Yes	No	No	0,004	Yes	No	No	0,042	Yes	No	No	-0,004	No	No	No
		Ln Direct marketing flow	-0,050	No	No	No	Removed (one non-zero observation only)				-0,199	No	No	No	Removed (two non-zero observations only)				0,102	Yes	No	No
	Competitive	Ln Competitive detailing flow	0,118	No	No	Yes	-0,036	Yes	No	No	0,096	No	No	No	-0,011	Yes	No	No	-0,051	Yes	No	No
		Ln Competitive journal advertising flow	0,007	No	No	Yes	0,003	No	No	No	-0,002	Yes	No	No	0,0004	No	No	No	-0,0001	Yes	No	No
		Ln Competitive direct marketing flow	-0,009	Yes	No	Yes	-0,008	Yes	Yes	Yes	-0,002	Yes	No	No	-0,003	Yes	No	No	0,004	No	No	No
Drug age		Drug age	-0,005	No	No	No	-0,020	No	No	No	0,018	Yes	No	No	0,008	Yes	No	No	-0,004	No	No	No
		Drug age squared	-0,0001	Yes	No	No	-0,0001	Yes	No	No	-0,0002	Yes	No	Yes	-0,0003	Yes	Yes	Yes	-0,0005	Yes	Yes	Yes
Interactions		Ln Journal advertising flow x Ln Detailing flow	0,016	---	Yes	Yes	-0,009	---	No	No	0,000	---	No	No	-0,006	---	No	No	0,002	---	No	No
		Ln Journal advertising flow x Ln Mailing flow	-0,001	---	No	No	No interactions in time series				-0,0004	---	No	No	0,000	---	No	No	-0,0019	---	No	No
		Ln Mailing flow x Ln Detailing flow	0,007	---	No	No	0,002	---	No	No	0,032	---	No	No	-0,001	---	No	No	-0,015	---	No	No
Temporal dummies		Quarter 2	0,056	---	No	No	0,139	---	Yes	Yes	0,072	---	No	Yes	0,114	---	Yes	Yes	0,153	---	Yes	Yes
		Quarter 3	0,214	---	Yes	Yes	0,226	---	Yes	Yes	0,163	---	Yes	Yes	0,150	---	Yes	Yes	0,266	---	Yes	Yes
		Quarter 4	0,239	---	No	Yes	0,361	---	Yes	Yes	0,204	---	Yes	Yes	0,236	---	Yes	Yes	0,414	---	Yes	Yes
		Year 2013	0,217	---	No	No	0,386	---	Yes	Yes	0,143	---	No	No	0,247	---	No	Yes	0,517	---	Yes	Yes
		Year 2014	0,537	---	No	No	0,801	---	Yes	Yes	0,440	---	No	No	0,498	---	No	Yes	0,876	---	Yes	Yes
		Year 2015	0,969	---	No	Yes	1,309	---	Yes	Yes	0,723	---	No	Yes	0,887	---	Yes	Yes	1,514	---	Yes	Yes
Adjusted R^2			0,320				0,409				0,408				0,925				0,587			
ANOVA Sig.			0,022				0,003				0,005				0,000				0,000			

10.4.3.2. Results

Based on the four tables shown above, we prepared a summary of results for a better interpretation, with table 10.37.

Table 10.37 – Summary of Wittink (2002) complete (Model 2) results

	Market 1 - Blood (3 products)				Market 2 - Pancreas (5 products)				Market 3 - Heart (5 products)				Market 4 - Liver (5 products)				Global (18 products)			
	% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities	
	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.
Ln Detailing flow	33,3%	0,0%	0,084	0,287	60,0%	0,0%	-0,006	0,058	100,0%	0,0%	0,018	0,018	60,0%	0,0%	0,008	0,060	66,7%	0,0%	0,020	0,061
Ln Journal advertising flow	66,7%	0,0%	0,112	0,183	20,0%	0,0%	-0,069	0,037	66,7%	0,0%	0,174	0,286	60,0%	0,0%	-0,003	0,035	50,0%	0,0%	0,031	0,135
Ln Direct marketing flow	33,3%	0,0%	-0,079	0,135	60,0%	0,0%	0,287	0,552	25,0%	0,0%	-0,208	0,009	33,3%	0,0%	-0,049	0,102	40,0%	0,0%	0,015	0,317
Ln Competitive detailing flow	66,7%	0,0%	-0,036	-0,071	20,0%	0,0%	0,140	-0,074	40,0%	0,0%	0,072	-0,058	60,0%	0,0%	0,023	-0,033	44,4%	0,0%	0,059	-0,054
Ln Competitive journal advertising flow	66,7%	0,0%	-0,001	-0,008	20,0%	0,0%	0,002	-0,004	40,0%	0,0%	0,002	-0,003	40,0%	0,0%	0,001	-0,001	38,9%	0,0%	0,001	-0,004
Ln Competitive direct marketing flow	0,0%	0,0%	0,012	N/A	80,0%	0,0%	0,004	-0,004	80,0%	20,0%	-0,002	-0,006	80,0%	20,0%	-0,004	-0,006	66,7%	11,1%	0,001	-0,005
Drug age	100,0%	100,0%	0,595	0,595	80,0%	0,0%	0,055	0,070	80,0%	20,0%	0,037	0,088	40,0%	0,0%	-0,001	0,013	72,2%	22,2%	0,125	0,188
Drug age squared	100,0%	100,0%	-0,006	-0,006	100,0%	0,0%	-0,001	-0,001	80,0%	80,0%	-0,001	-0,001	100,0%	40,0%	0,000	0,000	94,4%	50,0%	-0,001	-0,002
Ln Journal advertising flow x Ln Detailing flow	---	---	-0,022	---	---	---	0,009	---	---	---	-0,024	---	---	---	0,001	---	---	---	-0,005	---
Ln Journal advertising flow x Ln Mailing flow	---	---	0,001	---	---	---	0,001	---	---	---	0,002	---	---	---	-0,001	---	---	---	0,0005	---
Ln Mailing flow x Ln Detailing flow	---	---	0,011	---	---	---	-0,039	---	---	---	0,028	---	---	---	0,005	---	---	---	-0,001	---
Public reimbursement	66,7%	66,7%	1,775	2,756	---	---	---	---	---	---	---	---	---	---	---	---	66,7%	66,7%	1,775	2,756
Loss of exclusivity	---	---	---	---	---	---	---	---	50,0%	0,0%	-0,038	-0,133	---	---	---	---	50,0%	0,0%	-0,038	-0,133

10.4.4. Rizzo (1999) (Model 3)

10.4.4.1. Procedures and outputs

By directly applying model 3 (Rizzo, 1999) to our data, we noted several multicollinearity problems. To exemplify, we show the outputs of products BL1, shown below in figure 10.22.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow x Ln Detailing flow (calls)	-,308[b]	-,185	,854	-,032	4,520E-5
	Ln Detailing stock x Ln Detailing stock (calls)	-3,191[b]	-1,787	,083	-,297	3,573E-5
	Drug age	3,976[b]	2,746	,010	,431	4,851E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Year 2014 (dummy), Ln Competitive detailing flow (calls), Ln Drug price x drug age, Year 2013 (dummy), Ln Detailing flow (calls), Ln Detailing stock (calls), Public reimbursement (dummy), Drug age^2, Ln Average competitors price per DDD, Ln Drug price x Ln Detailing stock, Ln Drug price x Ln Detailing flow, Ln Average drug price per DDD

Figure 10.22 – Excluded variables for product BL1 in model 3

Rizzo (1999) had noted, regarding his data, that some forms of the regressions (46 products) had evidenced multicollinearity problems (p. 97). We developed some additional regressions using the excluded variables, to investigate the potential reasons by which SPSS was rejecting some variables. We started by regressing Ln Detailing flow x Ln detailing flow on Ln detailing flow. The results are shown below in figure 10.23.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,968[a]	,937	,937	4,508365992

a. Predictors: (Constant), Ln Detailing flow (calls)

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	242081,788	1	242081,788	11910,330	,000[b]
	Residual	16341,593	804	20,325		
	Total	258423,380	805			

a. Dependent Variable: Ln Detailing flow x Ln Detailing flow (calls)

b. Predictors: (Constant), Ln Detailing flow (calls)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-7,342	,538		-13,635	,000
	Ln Detailing flow (calls)	8,411	,077	,968	109,134	,000

a. Dependent Variable: Ln Detailing flow x Ln Detailing flow (calls)

Figure 10.23 – Linear regression of Ln Detailing flow x Ln Detailing flow on Ln Detailing flow for product BL1 in model 3

The output variable can be calculated almost perfectly using the original variable itself (Ln Detailing flow).

We performed a similar analysis regarding another pair of variables: Ln Detailing stock x Ln Detailing stock and Ln Detailing stock, whose outputs are shown in figure 10.24.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,989[a]	,978	,978	2,851083919

a. Predictors: (Constant), Ln Detailing stock (calls)

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	287953,821	1	287953,821	35424,428	,000[b]
	Residual	6535,458	804	8,129		
	Total	294489,279	805			

a. Dependent Variable: Ln Detailing stock x Ln Detailing stock (calls)

b. Predictors: (Constant), Ln Detailing stock (calls)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-31,007	,504		-61,519	,000
	Ln Detailing stock (calls)	12,052	,064	,989	188,214	,000

a. Dependent Variable: Ln Detailing stock x Ln Detailing stock (calls)

Figure 10.24 – Linear regression of Ln Detailing stock x Ln Detailing stock on Ln Detailing stock

Likewise, the output variable can be calculated almost perfectly using the original variable itself (Ln Detailing stock).

Finally, we regressed Drug age x Drug age on Drug age, and found, again, a very strong linear relation between the two variables, here shown in figure 10.25:

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,971[a]	,943	,943	2207,994510

a. Predictors: (Constant), Drug age

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	6,436E+10	1	6,436E+10	13202,302	,000[b]
	Residual	3919692764	804	4875239,757		
	Total	6,828E+10	805			

a. Dependent Variable: Drug age^2

b. Predictors: (Constant), Drug age

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-7148,899	153,111		-46,691	,000
	Drug age	196,629	1,711	,971	114,901	,000

a. Dependent Variable: Drug age^2

Figure 10.25 – Linear regression of Drug age x Drug age on Drug age for product BL1 in model 3

Our interpretation of these results is the following: there is a very high level of multicollinearity explained by the fact that the variables exhibit values in a very limited range, for which SPSS calculates a very close relation between the original values and the values multiplied by themselves. Given this multicollinearity problem, and in order to avoid multiple sets of excluded variables, we opted to use a slightly adapted Rizzo (1999) model, removing from the list of independent variables three variables:

- Ln Detailing flow x Ln Detailing flow
- Ln Detailing stock x Ln Detailing stock
- Drug age squared

Then testing this adapted model for product BL1, SPSS did not exclude any variable. However, running the regressions for the other products, we noticed that another variable was consistently being excluded: Ln Drug price x Ln Detailing stock. An example of product BL2 is shown below in figure 10.26.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing stock	-1,847[b]	-,616	,542	-,105	4,297E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Detailing flow (calls), Year 2013 (dummy), Ln Detailing stock (calls), Ln Competitive detailing flow (calls), Public reimbursement (dummy), Ln Average drug price per DDD, Year 2014 (dummy), Ln Drug price x drug age, Ln Average competitors price per DDD, Drug age, Ln Drug price x Ln Detailing flow

Figure 10.26 – Additional excluded variable for product BL2 in adjusted model 3

By regressing Ln Drug price x Ln Detailing stock on Ln Drug price, we obtained an almost linear combination which explains a very high amount of the variation of the dependent variable (here shown in figure 10.27).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,955[a]	,912	,912	1,759849674

a. Predictors: (Constant), Ln Average drug price per DDD

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	25944,104	1	25944,104	8376,981	,000[b]
	Residual	2490,045	804	3,097		
	Total	28434,149	805			

a. Dependent Variable: Ln Drug price x Ln Detailing stock

b. Predictors: (Constant), Ln Average drug price per DDD

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	,641	,062		10,259	,000
	Ln Average drug price per DDD	6,883	,075	,955	91,526	,000

a. Dependent Variable: Ln Drug price x Ln Detailing stock

Figure 10.27 – Linear regression of Ln Drug price x Ln Detailing stock on Ln Drug price for product BL2 in adjusted model 3

Again, to avoid exclusion of variables due to this multicollinearity issues, we decided to remove this interaction variable from the original Rizzo (1999) model for product BL2. Running the regressions again, no variables were excluded.

Regarding product BL3, we had to further adapt the model, again due to multicollinearity. We removed the interaction variables Ln average drug price x Ln Detailing flow and Ln average drug price x Drug age, given their very high correlation with the variables Ln average drug price and Drug age. By memory, product BL3 only has 18 observations (from July 2014 to December 2015).

In relation to product PA4, whose sales started in April 2013, we had to make some adjustment to the Rizzo (1999) model too. The first one was the removal of the variable Ln average drug price, given that, during the period of analysis, the drug did not experience any price change (constant). Therefore, the interaction variables Ln Drug price x Ln Detailing flow and Ln Drug price x Drug age had to be removed too.

Concerning product HE1, SPSS excluded the variable Ln average drug price x Drug age, given that there is an almost perfect correlation (-0,962) between the individual variables, as seen below in figure 10.28. Therefore, we removed this interaction variable from the regression model.

Correlations

		Drug age	Ln Average drug price per DDD
Drug age	Pearson Correlation	1	-,962**
	Sig. (2-tailed)		,000
	N	48	48
Ln Average drug price per DDD	Pearson Correlation	-,962**	1
	Sig. (2-tailed)	,000	
	N	48	48

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 10.28 – Correlation between Ln average drug price and Drug age for product HE1 in adjusted model 3

The same was done regarding products HE3, HE4, LI1 and LI2 which evidenced the same correlation problem between the same two variables, as seen below in figures 10.29, 10.30, 10.31, and 10.32.

Correlations

		Drug age	Ln Average drug price per DDD
Drug age	Pearson Correlation	1	-,877**
	Sig. (2-tailed)		,000
	N	48	48
Ln Average drug price per DDD	Pearson Correlation	-,877**	1
	Sig. (2-tailed)	,000	
	N	48	48

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 10.29 – Correlation between Ln average drug price and Drug age for product HE3

Correlations

		Drug age	Ln Average drug price per DDD
Drug age	Pearson Correlation	1	-,830**
	Sig. (2-tailed)		,000
	N	48	48
Ln Average drug price per DDD	Pearson Correlation	-,830**	1
	Sig. (2-tailed)	,000	
	N	48	48

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 10.30 – Correlation between Ln average drug price and Drug age for product HE4 in adjusted model 3

Correlations

		Drug age	Ln Average drug price per DDD
Drug age	Pearson Correlation	1	-,813**
	Sig. (2-tailed)		,000
	N	48	48
Ln Average drug price per DDD	Pearson Correlation	-,813**	1
	Sig. (2-tailed)	,000	
	N	48	48

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 10.31 – Correlation between Ln average drug price and Drug age for product LI1 in adjusted model 3

Correlations

		Drug age	Ln Average drug price per DDD
Drug age	Pearson Correlation	1	-,904**
	Sig. (2-tailed)		,000
	N	48	48
Ln Average drug price per DDD	Pearson Correlation	-,904**	1
	Sig. (2-tailed)	,000	
	N	48	48

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 10.32 – Correlation between Ln average drug price and Drug age for product LI2 in adjusted model 3

Product LI4 also evidenced some multicollinearity issues in the regressions, where we had to exclude Ln average drug price, given that it is almost a constant, with only a slight reduction of 0,5% in the drug price from January 2012 to December 2015. Therefore, the interaction variables Ln Drug price x Ln Detailing flow and Ln Drug price x Drug age also had to be removed. Figure 10.33 evidences the descriptive statistics for product LI4.

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Ln Average drug price per DDD	48	-,662149	-,657012	-,65988440	,001260072
Valid N (listwise)	48				

Figure 10.33 – Descriptive statistics of variable Ln average drug price for product LI4

After all these adptations to the Rizzo (1999) model, we show the summary tables such as with the previous two models, here shown in tables 10.38, 10.39, 10.40, and 10.41.

Table 10.38 – Summary of Rizzo (1999) (Model 3) regression outputs – Market 1 - Blood

Model specification			Rizzo (1999) (adapted)											
			Product BL1				Product BL2				Product BL3			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			6,606	---	Yes	Yes	14,433	---	Yes	Yes	12,964	---	No	No
Marketing expenditures flow	Own	Ln Detailing flow	0,028	Yes	No	No	0,435	Yes	No	No	0,239	Yes	No	Yes
	Competitive	Ln Competitive detailing flow	0,091	No	No	No	0,047	No	No	No	-0,097	No	No	No
Marketing expenditures stock		Ln Detailing stock	0,174	Yes	No	No	-0,004	No	No	No	0,639	Yes	Yes	Yes
Price	Own	Ln average drug price	0,004	No	No	No	-3,660	Yes	No	No	0,047	No	No	No
	Competitors	Ln Average competitors drug price	-1,542	No	No	No	-0,178	No	No	No	-14,437	No	Yes	Yes
Drug age		Drug age	0,070	Yes	Yes	Yes	-0,110	No	Yes	Yes	0,031	Yes	No	No
Marketing expenditures interactions		Ln Drug price x Ln Detailing flow	-0,007	No	No	No	-0,376	No	No	No	Removed due to multicollinearity			
		Ln Drug price x Drug age	-0,002	Yes	No	No	0,140	No	Yes	Yes				
Policy change		Public reimbursement	0,519	Yes	Yes	Yes	-0,104	No	No	No	4,263	Yes	Yes	Yes
Temporal dummies		Year 2013	-0,102	---	No	No	0,030	---	No	No	N/A (product launched in 2014)			
		Year 2014	-0,298	---	No	Yes	0,225	---	No	Yes				
		Year 2015	-0,119	---	No	No	0,137	---	No	No	0,147	---	No	No
Adjusted R^2			0,995				0,982				0,998			
ANOVA Sig.			0,000				0,000				0,000			

Source: own elaboration

Table 10.39 – Summary of Rizzo (1999) (Model 3) regression outputs – Market 2 – Pancreas

Model specification			Rizzo (1999) (adapted)																			
			Product PA1				Product PA2				Product PA3				Product PA4				Product PA5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			15,779	---	Yes	Yes	21,110	---	Yes	Yes	7,376	---	No	Yes	55,771	---	No	No	11,223	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	0,206	Yes	No	No	-0,316	No	No	No	0,608	Yes	No	No	0,057	Yes	No	No	0,143	Yes	No	No
	Competitive	Ln Competitive detailing flow	0,050	No	No	No	0,056	No	No	No	0,128	No	Yes	Yes	0,224	No	No	No	0,059	No	No	No
Marketing expenditures stock		Ln Detailing stock	0,073	Yes	No	No	-0,088	No	No	No	0,154	Yes	No	No	0,830	Yes	Yes	Yes	0,027	Yes	No	No
Price	Own	Ln average drug price	2,651	No	No	No	-25,749	Yes	No	No	13,104	No	No	No	Constant (no variation)				4,354	No	No	No
	Competitors	Ln Average competitors drug price	-12,689	No	No	No	1,679	Yes	No	No	-0,518	No	No	No	-285,5	No	No	No	-1,915	No	No	No
Drug age		Drug age	-0,027	No	No	Yes	-0,026	No	No	No	-0,020	No	No	No	0,124	Yes	Yes	Yes	0,020	Yes	No	No
Marketing expenditures interactions		Ln Drug price x Ln Detailing flow	-0,642	No	No	No	1,211	Yes	No	No	-2,191	No	No	No	Constant (no variation)				-0,344	No	No	No
		Ln Drug price x Drug age	0,125	No	Yes	Yes	0,107	No	No	No	0,096	No	No	No	Constant (no variation)				-0,057	Yes	No	No
Temporal dummies		Year 2013	-0,088	---	No	No	-0,103	---	No	Yes	-0,010	---	No	No	N/A (product launched in 2013)				-0,070	---	No	No
		Year 2014	-0,441	---	No	No	-0,427	---	No	No	0,013	---	No	No	-0,292	---	No	No	-0,210	---	No	No
		Year 2015	-0,501	---	No	No	-0,503	---	No	No	-0,014	---	No	No	-0,539	---	No	No	-0,259	---	No	No
Adjusted R^2			0,583				0,453				0,738				0,957				0,232			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,030			

Source: own elaboration

Table 10.40 – Summary of Rizzo (1999) (Model 3) regression outputs – Market 3 – Heart

Model specification			Rizzo (1999) (adapted)																	
			Product HE1				Product HE2				Product HE3				Product HE4				Product HE5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			12,252	---	No	Yes	9,916	---	Yes	Yes	15,594	---	Yes	Yes	18,411	---	Yes	Yes	-3,347	---	No	No
Marketing expenditures flow	Own	Ln Detailing flow	0,049	Yes	No	No	0,180	Yes	No	No	-0,027	No	No	No	-0,055	No	No	No	0,806	Yes	No	No
	Competitive	Ln Competitive detailing flow	0,021	No	No	No	-0,019	No	No	No	0,136	No	No	Yes	-0,057	Yes	No	No	0,150	No	No	No
Marketing expenditures stock		Ln Detailing stock	0,054	Yes	No	No	0,155	Yes	No	No	0,052	Yes	No	No	0,015	Yes	No	No	0,218	Yes	Yes	Yes
Price	Own	Ln average drug price	-1,002	Yes	No	No	-1,704	No	No	No	-0,556	Yes	No	No	1,268	No	No	Yes	-8,919	Yes	No	No
	Competitors	Ln Average competitors drug price	-0,402	No	No	Yes	-0,507	No	No	No	0,274	Yes	No	No	-1,307	No	No	Yes	-3,187	No	Yes	Yes
Drug age		Drug age	0,009	Yes	No	No	0,045	Yes	No	No	-0,014	No	No	Yes	-0,018	No	Yes	Yes	0,114	Yes	Yes	Yes
Marketing expenditures interactions		Ln Drug price x Ln Detailing flow	0,073	Yes	No	No	0,120	Yes	No	No	-0,026	No	No	No	-0,053	No	No	No	0,850	Yes	No	No
		Ln Drug price x Drug age	Removed due to multicollinearity				0,035	No	No	No	Removed due to multicollinearity				Removed due to multicollinearity				0,065	No	No	No
Policy change		Loss of exclusivity	Not applicable				Not applicable				-0,194	Yes	Yes	Yes	-0,112	Yes	No	Yes	Not applicable			
Temporal dummies		Year 2013	-0,048	---	No	No	-0,022	---	No	Yes	0,042	---	No	Yes	-0,353	---	Yes	Yes	N/A (product launched in 2013)			
		Year 2014	-0,067	---	No	No	-0,015	---	No	No	0,103	---	No	No	-0,431	---	Yes	Yes	0,115	---	No	No
		Year 2015	-0,100	---	No	No	0,383	---	No	No	-0,093	---	No	No	-0,334	---	Yes	Yes	-0,123	---	No	No
Adjusted R^2			0,768				0,423				0,913				0,975				0,980			
ANOVA Sig.			0,000				0,001				0,000				0,000				0,000			

Source: own elaboration

Table 10.41 – Summary of Rizzo (1999) (Model 3) regression outputs – Market 4 – Liver

Model specification			Rizzo (1999) (adapted)																	
			Product LI1				Product LI2				Product LI3				Product LI4				Product LI5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			14,952	---	No	No	13,473	---	No	Yes	17,462	---	No	Yes	11,781	---	Yes	Yes	16,936	---	Yes	Yes
Marketing expenditures flow	Own	Ln Detailing flow	-0,035	No	No	No	0,006	Yes	No	No	-0,578	No	No	No	0,074	Yes	No	No	-0,251	No	No	No
	Competitive	Ln Competitive detailing flow	0,110	No	No	No	0,022	No	No	No	0,143	No	No	Yes	-0,006	Yes	No	No	0,032	No	No	No
Marketing expenditures stock		Ln Detailing stock	-0,133	No	No	No	0,012	Yes	No	No	0,092	Yes	No	No	0,075	Yes	No	No	0,277	Yes	Yes	Yes
Price	Own	Ln average drug price	0,043	No	No	No	-1,319	Yes	No	No	9,332	No	No	No	Removed (almost constant)				-12,897	Yes	No	Yes
	Competitors	Ln Average competitors drug price	0,772	Yes	No	Yes	0,185	Yes	No	No	-0,628	No	No	No	-0,743	No	No	No	0,752	Yes	Yes	Yes
Drug age		Drug age	0,005	Yes	No	No	0,003	Yes	No	No	-0,028	No	No	No	0,017	Yes	Yes	Yes	-0,108	No	Yes	Yes
Marketing expenditures interactions		Ln Drug price x Ln Detailing flow	-0,106	No	No	No	0,013	Yes	No	No	-1,078	No	No	No	Removed (almost constant)				0,452	Yes	No	No
		Ln Drug price x Drug age	Removed due to multicollinearity				Removed due to multicollinearity				-0,045	Yes	No	No	Removed (almost constant)				0,193	No	Yes	Yes
Temporal dummies		Year 2013	-0,122	---	Yes	Yes	-0,023	---	No	No	-0,011	---	No	No	0,054	---	No	No	-0,057	---	No	No
		Year 2014	-0,099	---	No	No	-0,031	---	No	No	0,058	---	No	No	-0,031	---	No	No	-0,169	---	No	No
		Year 2015	-0,135	---	No	No	-0,071	---	No	No	0,059	---	No	No	-0,038	---	No	No	-0,207	---	No	No
Adjusted R^2			0,089				0,253				0,278				0,898				0,690			
ANOVA Sig.			0,195				0,017				0,014				0,000				0,000			

Source: own elaboration

10.4.4.2. Results

Based on the four tables shown above, we prepared a summary of results for a better interpretation, in table 10.42.

Table 10.42 – Summary of Rizzo (1999) (Model 3) results

	Market 1 - Blood (3 products)				Market 2 - Pancreas (5 products)				Market 3 - Heart (5 products)				Market 4 - Liver (5 products)				Global (18 products)			
	% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities	
	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.
Ln Detailing flow	100,0%	0,0%	0,234	0,234	80,0%	0,0%	0,140	0,254	60,0%	0,0%	0,191	0,345	40,0%	0,0%	-0,157	0,040	66,7%	0,0%	0,087	0,236
Ln Competitive detailing flow	0,0%	0,0%	0,014	-0,097	0,0%	0,0%	0,103	N/A	20,0%	0,0%	0,046	-0,038	20,0%	0,0%	0,060	-0,006	11,1%	0,0%	0,061	-0,045
Ln Detailing stock	66,7%	33,3%	0,270	0,407	80,0%	20,0%	0,199	0,271	100,0%	20,0%	0,099	0,099	80,0%	20,0%	0,065	0,114	83,3%	22,2%	0,146	0,190
Ln average drug price	33,3%	0,0%	-1,203	-3,660	25,0%	0,0%	-1,410	-25,749	60,0%	0,0%	-2,183	-3,045	50,0%	0,0%	-1,210	4,688	43,8%	0,0%	-1,563	-4,027
Ln average competitors drug price	0,0%	0,0%	-5,385	N/A	20,0%	0,0%	-59,795	1,679	20,0%	0,0%	-1,026	0,274	60,0%	20,0%	0,067	0,570	27,8%	5,6%	-17,773	0,732
Drug age	66,7%	33,3%	-0,003	0,051	40,0%	20,0%	0,014	0,072	60,0%	20,0%	0,027	0,056	60,0%	20,0%	-0,022	0,008	55,6%	22,2%	0,005	0,044
Ln average drug price x Ln Detailing flow	0,0%	0,0%	-0,191	N/A	25,0%	0,0%	-0,492	1,211	60,0%	0,0%	0,193	0,348	50,0%	0,0%	-0,180	0,233	40,0%	0,0%	-0,140	0,453
Ln average drug price x Drug age	50,0%	0,0%	0,069	-0,002	25,0%	0,0%	0,068	-0,057	0,0%	0,0%	0,050	N/A	50,0%	0,0%	0,074	-0,045	30,0%	0,0%	0,066	-0,035
Public reimbursement	66,7%	66,7%	1,559	2,391	---	---	---	---	---	---	---	---	---	---	---	---	66,7%	66,7%	1,559	2,391
Loss of exclusivity	---	---	---	---	---	---	---	---	100,0%	50,0%	-0,153	-0,153	---	---	---	---	100,0%	50,0%	-0,153	-0,153

Source: own elaboration

10.4.5. Windmeijer et al (2006) (Model 4)

10.4.5.1. Procedures and outputs

Starting with product BL1, SPSS outputs excluded the variable Ln Average drug price (here shown in figure 10.34). We performed manual investigation to try to understand the reason for the exclusion.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	3,534[b]	1,390	,175	,254	9,689E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Year 2014 (dummy), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Year 2013 (dummy), Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures flow, Ln Global marketing expenditures stock, Public reimbursement (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Ln Global marketing expenditures stock x Ln Average drug price, Ln Sales in DDDs lagged two periods, Drug age^2, Ln Sales in DDDs lagged one period, Drug age, Ln Average competitors price per DDD

Figure 10.34 – Excluded variables for product BL1 in model 4

We noted that Ln Average drug price can be calculated, to a very good extent, through a linear combination of product BL1 competitors' average drug price and a dummy variable, as seen below in figure 10.35.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,973[a]	,946	,944	,088143584

a. Predictors: (Constant), Public reimbursement (dummy), Ln Average competitors price per DDD

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	6,172	2	3,086	397,201	,000[b]
	Residual	,350	45	,008		
	Total	6,522	47			

a. Dependent Variable: Ln Average drug price per DDD

b. Predictors: (Constant), Public reimbursement (dummy), Ln Average competitors price per DDD

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-,702	,152		-4,604	,000
	Ln Average competitors price per DDD	1,991	,137	,674	14,524	,000
	Public reimbursement (dummy)	-,296	,036	-,384	-8,267	,000

a. Dependent Variable: Ln Average drug price per DDD

Figure 10.35 – Linear regression of Ln Average competitors price on Ln Average drug price and policy change dummy, for product BL1 in model 4

This is likely the reason for variable exclusion in the SPSS outputs. Therefore, in the presence of this multicollinearity, we removed the variable Ln Average competitors' price from the model. Running the regression again without this variable resulted in no variables exclusion.

Running the full model 4 regression for product BL2, SPSS excluded the two interaction variables (figure 10.36).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	1,981[b]	,459	,650	,085	1,982E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	4,012[b]	,968	,341	,177	2,096E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures flow, Year 2013 (dummy), Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Quarter 3 (dummy), Ln Global marketing expenditures stock, Public reimbursement (dummy), Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Average competitors price per DDD, Ln Sales in DDDs lagged one period, Drug age^2, Drug age

Figure 10.36 – Excluded variables for product BL2 in model 4

This is due to the multicollinearity, where the interaction variables are almost a perfect linear combination of the two individual variables. Below we can see this situation for the variable Ln Global marketing expenditures stock x Ln Average drug price (figure 10.37).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	1,000[a]	1,000	1,000	,014318747

a. Predictors: (Constant), Ln Average drug price per DDD, Ln Global marketing expenditures stock

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	141,327	2	70,664	344655,519	,000[b]
	Residual	,009	45	,000		
	Total	141,336	47			

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average drug price

b. Predictors: (Constant), Ln Average drug price per DDD, Ln Global marketing expenditures stock

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-13,465	,242		-55,673	,000
	Ln Global marketing expenditures stock	1,012	,020	,093	51,061	,000
	Ln Average drug price per DDD	13,311	,026	,929	511,415	,000

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average drug price

Figure 10.37 – Linear regression of Ln Global marketing expenditures stock x Ln Average drug price on Ln Global marketing expenditures stock and Ln Average drug price, for product BL2 in model 4

Given this multicollinearity problem, we decided to remove the two interaction variables from the equation for product BL2. The updated regression outputs for BL2 did not exclude any variable.

Product BL3 outputs evidenced three excluded variables, show below (figure 10.38).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-10,501[b]	-,761	,526	-,474	4,238E-7
	Ln Average competitors price per DDD	-14,230[b]	-1,279	,329	-,671	4,623E-7
	Drug age	1,952[b]	,463	,689	,311	5,295E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Global marketing expenditures flow, Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 2 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Ln Competitive global marketing expenditures flow, Public reimbursement (dummy), Ln Competitive global marketing expenditures stock, Quarter 3 (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Drug age^2, Ln Global marketing expenditures stock

Figure 10.38 – Excluded variables for product BL3 in model 4 – iteration 1

In an attempt to find the reasons for this exlusion, we mannualy investigated some regression models, starting with Drug age dependent on Drug age squared (figure 10.39).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,998[a]	,996	,996	,329492559

a. Predictors: (Constant), Drug age^2

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	482,763	1	482,763	4446,750	,000[b]
	Residual	1,737	16	,109		
	Total	484,500	17			

a. Dependent Variable: Drug age

b. Predictors: (Constant), Drug age^2

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	18,971	,303		62,612	,000
	Drug age^2	,013	,000	,998	66,684	,000

a. Dependent Variable: Drug age

Figure 10.39 – Linear regression of Drug age on Drug age squared, for product BL3 in model 4

In this time series, which as seen before includes 18 observations (months), drug age can be almost perfectly calculated with drug age squared. We decided, therefore, to remove drug age squared from the regression. However, SPSS continued excluding two variables, as seen below in figure 10.40.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-11,676[b]	-,864	,479	-,521	4,057E-7
	Ln Average competitors price per DDD	-16,205[b]	-1,586	,254	-,746	4,317E-7

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Global marketing expenditures flow, Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 2 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Ln Competitive global marketing expenditures flow, Public reimbursement (dummy), Ln Competitive global marketing expenditures stock, Quarter 3 (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Drug age, Ln Global marketing expenditures stock

Figure 10.40 – Excluded variables for product BL3 in model 4 – iteration 2

Based on our experience with the two previous products, the regression for product BL3 must be experiencing multicollinearity between the interaction variables and the individual variables on their basis. We tested this suspicion with the first interaction variable (figure 10.41).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,995[a]	,991	,989	,042748327

a. Predictors: (Constant), Ln Average drug price per DDD, Ln Global marketing expenditures stock

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	2,863	2	1,431	783,264	,000[b]
	Residual	,027	15	,002		
	Total	2,890	17			

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average drug price

b. Predictors: (Constant), Ln Average drug price per DDD, Ln Global marketing expenditures stock

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-10,329	,612		-16,886	,000
	Ln Global marketing expenditures stock	,892	,030	1,238	29,376	,000
	Ln Average drug price per DDD	11,536	,293	1,661	39,400	,000

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average drug price

Figure 10.41 – Linear regression of Ln Global marketing expenditures stock x Ln Average drug price on Ln Global marketing expenditures stock and Ln Average drug price, for product BL3 in model 4

As expected, the interaction variable is substantially dependent on its two individual variables. We decided to remove both interaction variables, and as a consequence no additional variable was excluded by SPSS.

Regarding product PA1, SPSS excluded the two variables, shown below in figure 10.42.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	16,958[b]	,606	,549	,110	8,880E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	27,849[b]	1,063	,296	,191	9,874E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures flow, Year 2013 (dummy), Quarter 3 (dummy), Ln Average drug price per DDD, Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Global marketing expenditures stock, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Drug age, Ln Average competitors price per DDD

Figure 10.42 – Excluded variables for product PA1 in model 4

We decided to remove these two variables from the regression, given that, as seen before, the interaction variables can be calculated almosted perfectly through a linear combination of the individual variables on their basis.

In the case of product PA2, two variables were excluded by SPSS, as seen in figure 10.43.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	-23,041[b]	-,721	,477	-,130	6,893E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	-27,884[b]	-,921	,365	-,166	7,597E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Competitive global marketing expenditures flow, Year 2013 (dummy), Quarter 2 (dummy), Ln Competitive global marketing expenditures stock, Quarter 3 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Average competitors price per DDD, Ln Global marketing expenditures flow, Ln Global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Drug age, Ln Average drug price per DDD

Figure 10.43 – Excluded variables for product PA2 in model 4

Given the reasons presented before, we decided to remove these two variables from the regression model, to avoid multicollinearity.

In the case of product PA3, SPSS excluded, once again, the two interaction variables (figure 10.44).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	-6,953[b]	-,553	,584	-,100	2,425E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	-8,595[b]	-,717	,479	-,130	2,651E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock, Ln Global marketing expenditures flow, Quarter 3 (dummy), Year 2014 (dummy), Quarter 2 (dummy), Year 2013 (dummy), Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Average competitors price per DDD, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Average drug price per DDD, Drug age

Figure 10.44 – Excluded variables for product PA3 in model 4

The reason for that is due to the almost perfect ability of obtaining the interaction variables based on their decomposition of the two separate variables, as covered before.

In the case of product PA4, we removed the variable Ln Average drug price since it is a constant (zero variation through the months). Then two variables were excluded by SPSS, as displayed below in figure 10.45.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	-39,947[b]	-,862	,401	-,205	6,398E-7
	Ln Global marketing expenditures stock x Ln Average drug price	-39,788[b]	-,857	,404	-,203	6,372E-7

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Ln Global marketing expenditures flow, Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Year 2014 (dummy), Drug age^2, Drug age

Figure 10.45 – Excluded variable for product PA4 in model 4 – iteration 1

Such as seen in previous examples, this is explained by the almost perfect linear explanation of the interaction variable based on its two base, original variables. Therefore we decided to remove the interaction variable. SPSS then kept excluding the variable Ln Global marketing expenditures stock (figure 10.46).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	-39,947[b]	-,862	,401	-,205	6,398E-7

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Ln Global marketing expenditures flow, Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Year 2014 (dummy), Drug age^2, Drug age

Figure 10.46 – Excluded variable for product PA4 in model 4 – iteration 2

After a further investigation, we noticed that the likely reason for this exclusion is very high multicollinearity between the interaction variable Ln Marketing expenditures stock x Ln Average competitors' price, and its two base variables. The output is shown below in figure 10.47:

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	1,000[a]	1,000	1,000	,000191721

a. Predictors: (Constant), Ln Average competitors price per DDD, Ln Global marketing expenditures stock

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	,153	2	,077	2082150,142	,000[b]
	Residual	,000	30	,000		
	Total	,153	32			

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average competitors price

b. Predictors: (Constant), Ln Average competitors price per DDD, Ln Global marketing expenditures stock

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-2,592	,011		-245,957	,000
	Ln Global marketing expenditures stock	,198	,000	1,037	1993,107	,000
	Ln Average competitors price per DDD	13,118	,051	,134	258,069	,000

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average competitors price

Figure 10.47 – Linear regression of Ln Global marketing expenditures stock x Ln Average competitors' price on Ln Global marketing expenditures stock and Ln Average competitors price, for product PA4 in model 4

Therefore, by removing this interaction variable from the equation, SPSS outputs did not evidence any additional excluded variables.

Moving to product PA5, two variables were excluded by SPSS: Ln Average drug price and Ln Average competitors' price (figure 10.48).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-21,506[b]	-1,434	,162	-,253	6,015E-5
	Ln Average competitors price per DDD	-31,910[b]	-2,192	,036	-,372	5,876E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Sales in DDDs lagged two periods, Year 2013 (dummy), Ln Sales in DDDs lagged one period, Quarter 2 (dummy), Ln Global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Ln Global marketing expenditures stock x Ln Average drug price, Drug age

Figure 10.48 – Excluded variables for product PA5 in model 4 – iteration 1

The reason for this was, once more, the multicollinearity between the interaction variables and their individual variables. In the case of the first interaction variable, the outputs below confirm our suspicions (figure 10.49).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	1,000[a]	1,000	1,000	,003757211

a. Predictors: (Constant), Ln Average competitors price per DDD, Ln Global marketing expenditures stock

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	5,050	2	2,525	178852,601	,000[b]
	Residual	,001	45	,000		
	Total	5,050	47			

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average competitors price

b. Predictors: (Constant), Ln Average competitors price per DDD, Ln Global marketing expenditures stock

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-3,272	,055		-59,606	,000
	Ln Global marketing expenditures stock	,272	,004	,129	64,417	,000
	Ln Average competitors price per DDD	12,036	,023	1,065	532,410	,000

a. Dependent Variable: Ln Global marketing expenditures stock x Ln Average competitors price

Figure 10.49 – Linear regression of Ln Global marketing expenditures stock x Ln Average competitors' price on Ln Global marketing expenditures stock and Ln Average competitors' price, for product PA5 in model 4

We started by removing this interaction variable and ran the regression again. SPSS excluded Ln Average drug price (figure 10.50).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-21,693[b]	-1,400	,172	-,248	5,642E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Sales in DDDs lagged two periods, Year 2013 (dummy), Ln Sales in DDDs lagged one period, Quarter 2 (dummy), Ln Global marketing expenditures flow, Year 2014 (dummy), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock, Ln Average competitors price per DDD, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Global marketing expenditures stock x Ln Average drug price, Drug age

Figure 10.50 – Excluded variables for product PA5 in model 4 – iteration 2

Then we decided to remove the other interaction variable (Ln Global marketing expenditures stock x Ln Average Drug price), and no issues with multicollinearity were detected.

Moving to product HE1, SPSS excluded the variable Ln Global marketing expenditures stock (figure 10.51).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	4,618[b]	,350	,729	,065	1,515E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 3 (dummy), Year 2014 (dummy), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures stock x Ln Average drug price, Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Average drug price per DDD, Drug age^2, Drug age, Ln Average competitors price per DDD

Figure 10.51 – Excluded variable for product HE1 in model 4

Our suspicion is that, by removing the interaction variable Ln Marketing expenditures stock x Ln Average drug price, collinearity problems will subside and no additional variable may be excluded, which turn out a right option.

In the case of product HE2, two variables were excluded by SPSS (figure 10.52).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	6,892[b]	,396	,695	,072	2,514E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	9,989[b]	,978	,336	,176	7,091E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Average competitors price per DDD, Quarter 3 (dummy), Year 2014 (dummy), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Global marketing expenditures stock, Drug age^2, Ln Global marketing expenditures stock x Ln Average drug price, Drug age

Figure 10.52 – Excluded variable for product HE2 in model 4 – iteration 1

We first removed the interaction variable and ran the regression again. However, the other variable was still excluded by SPSS (figure 10.53).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	6,892[b]	,396	,695	,072	2,514E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Average competitors price per DDD, Quarter 3 (dummy), Year 2014 (dummy), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Global marketing expenditures stock, Drug age^2, Ln Global marketing expenditures stock x Ln Average drug price, Drug age

Figure 10.53 – Excluded variable for product HE2 in model 4 – iteration 2

Therefore, we decided to remove the other interaction variable (Ln Global marketing expenditures stock x Ln Average Drug price), which solved the multicollinearity issue.

Regarding product HE3, SPSS excluded the variable Drug age (figure 10.54).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	,560[b]	,150	,882	,028	7,800E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Year 2014 (dummy), Quarter 3 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Year 2013 (dummy), Ln Global marketing expenditures flow, Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Loss of exclusivity (dummy), Ln Average competitors price per DDD, Ln Sales in DDDs lagged one period, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Sales in DDDs lagged two periods, Drug age^2, Ln Average drug price per DDD, Ln Global marketing expenditures stock

Figure 10.54 – Excluded variable for product HE3 in model 4

Given our previous experience on the likely issues of collinearity between Drug age and Drug age squared, we removed the latter from the regression and the issue subsided, with no further variables removed automatically by SPSS.

In the case of product HE4, two variables were excluded by SPSS (figure 10.55):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	-5,025[b]	-2,153	,040	-,371	6,048E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	,608[b]	,285	,778	,053	8,338E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Average competitors price per DDD, Quarter 3 (dummy), Year 2013 (dummy), Ln Global marketing expenditures flow, Quarter 2 (dummy), Year 2014 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Loss of exclusivity (dummy), Ln Average drug price per DDD, Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Drug age^2, Ln Global marketing expenditures stock

Figure 10.55 – Excluded variable for product HE4 in model 4

By removing the variables Drug age squared and Ln Global marketing expenditures stock x Ln Average competitors' price from the regression, SPSS did not exclude any additional variable.

In the case of product HE5, SPSS excluded two variables, shown below (figure 10.56).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	-10,893[b]	-2,905	,009	-,565	1,905E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	14,108[b]	1,155	,263	,263	2,456E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Global marketing expenditures stock, Ln Average drug price per DDD, Quarter 3 (dummy), Quarter 2 (dummy), Year 2014 (dummy), Ln Average competitors price per DDD, Ln Global marketing expenditures flow, Quarter 4 (dummy), Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Ln Sales in DDDs lagged one period, Drug age^2, Drug age

Figure 10.56 – Excluded variables for product HE5 in model 4

As performed in similar cases using Model 4, we decided to remove the two interaction variables, highly correlated with the variables they are based at.

Moving to Market Liver, SPSS excluded, in the case of product LI1, two variables (figure 10.57).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-,946[b]	-,037	,971	-,007	2,349E-5
	Ln Average competitors price per DDD	-16,713[b]	-,792	,435	-,143	3,457E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Sales in DDDs lagged two periods, Year 2014 (dummy), Ln Sales in DDDs lagged one period, Quarter 3 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Quarter 2 (dummy), Year 2013 (dummy), Ln Global marketing expenditures flow, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Global marketing expenditures stock, Drug age^2, Drug age

Figure 10.57 – Excluded variable for product LI1 in model 4

By manually removing the interaction variables in Model 4 for product LI1, no additional variables were excluded by SPSS.

Regarding product LI2, SPSS excluded the following two variables (figure 10.58):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	11,696[b]	,905	,373	,163	5,485E-5
	Ln Global marketing expenditures stock x Ln Average drug price	-16,474[b]	-,915	,368	-,165	2,822E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Year 2014 (dummy), Quarter 3 (dummy), Ln Sales in DDDs lagged one period, Ln Global marketing expenditures flow, Quarter 2 (dummy), Ln Competitive global marketing expenditures stock, Year 2013 (dummy), Ln Global marketing expenditures stock, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures flow, Ln Average drug price per DDD, Ln Global marketing expenditures stock x Ln Average competitors price, Drug age^2, Drug age

Figure 10.58 – Excluded variables for product LI2 in model 4

Given our experience using model 4, the multicollinearity is likely due to the almost perfect linear relation between the interaction variables and the two variables on their bases. We decided to remove both the interaction variables from the regression, which solved the multicollinearity issue.

Product LI3 also evidenced multicollinearity between the interaction variables and their base variables. SPSS rejected these two variables (figure 10.59):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-7,850[b]	-,579	,567	-,105	7,340E-5
	Ln Average competitors price per DDD	-16,438[b]	-1,134	,266	-,203	6,231E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock, Quarter 2 (dummy), Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Sales in DDDs lagged one period, Quarter 3 (dummy), Ln Sales in DDDs lagged two periods, Ln Global marketing expenditures stock x Ln Average drug price, Year 2014 (dummy), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Competitive global marketing expenditures stock, Drug age^2, Drug age

Figure 10.59 – Excluded variable for product LI3 in model 4

By removing the two interaction variables from the regression, the issue was solved.

In relation to product LI4, SPSS excluded the variable Ln Global marketing expenditures stock (figure 10.60).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	-12,589[b]	-,278	,783	-,052	5,909E-7

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Year 2014 (dummy), Quarter 3 (dummy), Year 2013 (dummy), Quarter 2 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Average drug price per DDD, Ln Competitive global marketing expenditures stock, Drug age^2, Drug age, Ln Average competitors price per DDD

Figure 10.60 – Excluded variable for product LI4 in model 4

Once again, given our experience with previous similar situations in model 4, we removed the interaction variable Ln Global marketing expenditures stock x Ln Average drug price, which solved the multicollinearity issue.

Finally, in the case of product LI5, SPSS excluded the two interaction variables (figure 10.61).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	21,915[b]	1,776	,086	,308	3,202E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	15,814[b]	1,487	,147	,262	4,438E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Competitive global marketing expenditures stock, Ln Sales in DDDs lagged one period, Quarter 2 (dummy), Year 2014 (dummy), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Global marketing expenditures stock, Ln Average drug price per DDD, Ln Average competitors price per DDD, Drug age^2, Drug age

Figure 10.61 – Excluded variables for product LI5 in model 4

As in previous similar situations using Model 4, we decided to remove the two interaction variables from the regression, in order to solve the multicollinearity issue. Tables 10.43, 10.44, 10.45, and 10.46 present a summary of the coefficients using Model 4.

Table 10.43 – Summary of Windmeijer et al (2006) – Market 1 - Blood

Model specification			Windmeijer et al (2006)											
			Product BL1				Product BL2				Product BL3			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			4,148	---	No	No	5,338	---	No	Yes	-8,945	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		0,208	Yes	No	No	-0,126	No	No	No	-0,048	No	No	No
	Ln Sales in DDDs lagged two periods		0,104	Yes	No	No	0,255	Yes	No	Yes	0,093	Yes	No	Yes
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	0,020	Yes	No	No	0,067	Yes	0,221	No	0,136	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	0,066	No	No	No	0,037	No	No	No	0,068	No	No	No
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	-0,148	No	No	No	0,166	Yes	No	No	0,171	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	0,324	No	Yes	Yes	0,037	No	No	No	0,974	No	No	No
Price	Own	Ln Average drug price per DDD	-2,506	Yes	No	No	-0,346	Yes	No	No	-0,003	No	No	No
	Competitors	Ln Average competitors drug price per DDD	Removed due to multicollinearity				-0,195	No	No	No	-7,656	No	No	No
Drug age		Drug age	0,026	Yes	No	No	0,076	Yes	No	No	0,089	Yes	No	Yes
		Drug age squared	-0,0001	Yes	No	No	-0,001	Yes	Yes	Yes	Removed due to multicollinearity			
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		0,189	Yes	No	No	Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		-0,113	Yes	Yes	Yes	Removed due to multicollinearity				Removed due to multicollinearity			
Policy change		Public reimbursement	0,367	Yes	Yes	Yes	-0,211	No	Yes	Yes	5,069	Yes	Yes	Yes
Temporal dummies		Quarter 2	0,061	---	No	No	0,067	---	No	No	-0,013	---	No	No
		Quarter 3	0,156	---	No	No	0,225	---	Yes	Yes	0,075	---	No	No
		Quarter 4	0,278	---	No	Yes	0,354	---	Yes	Yes	-0,014	---	No	No
		Year 2013	0,263	---	No	No	0,363	---	No		N/A (product launched in 2014)			
		Year 2014	0,547	---	No	No	0,818	---	Yes	Yes				
		Year 2015	0,970	---	No	No	1,253	---	Yes	Yes	0,188	---	No	No
Adjusted R^2			0,997				0,983				0,999			
ANOVA Sig.			0,000				0,000				0,000			

Table 10.44 – Summary of Windmeijer et al (2006) – Market 2 - Pancreas

Model specification			Windmeijer et al (2006)																	
			Product PA1				Product PA2				Product PA3				Product PA4				Product PA5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			19,260	---	Yes	Yes	27,719	---	Yes	Yes	16,276	---	Yes	Yes	12,687	---	No	No	16,833	---	Yes	Yes
Lagged sales	Ln Sales in DDDs lagged one period		-0,463	No	Yes	Yes	-0,512	No	Yes	Yes	-0,496	No	Yes	Yes	0,020	Yes	No	No	-0,425	No	Yes	Yes
	Ln Sales in DDDs lagged two periods		0,193	Yes	No	No	-0,084	No	No	No	0,041	No	No	No	-0,017	No	No	No	-0,111	No	No	No
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	0,032	Yes	No	No	0,021	Yes	No	No	-0,075	No	Yes	Yes	0,180	Yes	No	No	0,047	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	-0,032	Yes	No	No	-0,006	Yes	No	No	0,131	No	Yes	Yes	0,148	No	No	No	0,033	No	No	No
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	0,132	Yes	No	No	-0,210	No	No	Yes	0,103	Yes	No	No	0,548	Yes	No	No	0,050	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	0,010	No	No	No	0,145	No	No	No	-0,00001	Yes	No	No	0,656	No	No	No	0,239	No	No	No
Price	Own	Ln Average drug price per DDD	6,519	No	No	No	-17,215	Yes	No	Yes	3,299	No	No	No	Constant (no variation)				-5,274	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	-15,643	No	No	No	3,977	Yes	No	No	-0,373	No	No	No	-128,38	No	No	No	0,212	Yes	No	No
Drug age		Drug age	0,005	Yes	No	No	-0,003	No	No	No	0,013	Yes	No	No	0,191	Yes	Yes	Yes	-0,010	No	No	No
		Drug age squared	-0,0003	Yes	Yes	Yes	-0,0002	Yes	Yes	Yes	-0,0003	Yes	Yes	Yes	-0,002	Yes	No	No	0,00002	No	No	No
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Temporal dummies		Quarter 2	0,189	---	Yes	Yes	0,103	---	Yes	Yes	0,125	---	Yes	Yes	0,146	---	No	No	0,033	---	No	No
		Quarter 3	0,290	---	Yes	Yes	0,233	---	Yes	Yes	0,209	---	Yes	Yes	0,550	---	Yes	Yes	0,099	---	No	No
		Quarter 4	0,422	---	Yes	Yes	0,328	---	Yes	Yes	0,303	---	Yes	Yes	0,581	---	No	No	0,132	---	No	No
		Year 2013	0,437	---	Yes	Yes	0,337	---	Yes	Yes	0,337	---	Yes	Yes	N/A (product launched in 2013)				0,089	---	No	No
		Year 2014	0,451	---	No	No	0,165	---	No	No	0,764	---	Yes	Yes	0,600	---	No	No	0,021	---	No	No
		Year 2015	0,921	---	No	Yes	0,470	---	No	No	1,130	---	Yes	Yes	1,133	---	No	No	0,150	---	No	No
Adjusted R^2			0,680				0,674				0,824				0,957				0,350			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,011			

Table 10.45 – Summary of Windmeijer et al (2006) – Market 3 - Heart

Model specification			Windmeijer et al (2006)																			
			Product HE1				Product HE2				Product HE3				Product HE4				Product HE5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			22,962	---	Yes	Yes	20,740	---	Yes	Yes	0,972	---	No	Yes	21,106	---	Yes	Yes	3,727	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,764	No	Yes	Yes	-0,554	No	Yes	Yes	-0,073	No	No	No	-0,087	No	No	No	0,045	Yes	No	No
	Ln Sales in DDDs lagged two periods		-0,163	No	No	No	0,089	Yes	No	No	0,412	Yes	No	No	0,069	Yes	No	No	0,017	Yes	No	No
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	0,003	Yes	No	No	0,002	Yes	No	No	0,007	Yes	No	No	0,006	Yes	No	No	0,049	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	-0,053	Yes	No	Yes	-0,046	Yes	No	No	0,069	No	No	No	-0,044	Yes	No	No	0,019	No	No	No
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	0,418	Yes	No	Yes	0,159	Yes	No	No	1,614	Yes	No	Yes	0,819	Yes	Yes	Yes	0,046	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	-0,015	Yes	No	No	-0,056	Yes	No	No	0,146	No	No	No	-0,394	Yes	Yes	Yes	0,281	No	No	No
Price	Own	Ln Average drug price per DDD	0,068	No	No	No	0,445	No	No	No	4,153	No	No	Yes	-4,130	Yes	No	Yes	-0,127	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	-3,451	No	No	Yes	-0,287	No	No	No	-21,224	No	Yes	Yes	-1,132	No	No	Yes	-1,438	No	No	No
Drug age		Drug age	0,021	Yes	No	No	-0,003	No	No	No	-0,056	No	Yes	Yes	-0,042	No	Yes	Yes	0,083	Yes	Yes	Yes
		Drug age squared	0,000	N/A	Yes	Yes	-0,0002	Yes	No	Yes	Removed due to multicollinearity				Removed due to multicollinearity				-0,001	Yes	Yes	Yes
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				-0,552	No	No	Yes	0,634	Yes	Yes	Yes	Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		0,268	No	No	No	Removed due to multicollinearity				2,454	No	Yes	Yes	Removed due to multicollinearity				Removed due to multicollinearity			
Policy change	Loss of exclusivity		Not applicable				Not applicable				-0,091	Yes	No	No	-0,161	Yes	Yes	Yes	Not applicable			
Temporal dummies	Quarter 2		0,107	---	Yes	Yes	0,121	---	Yes	Yes	0,128	---	No	No	0,063	---	No	No	0,057	---	No	No
	Quarter 3		0,170	---	Yes	Yes	0,183	---	Yes	Yes	0,258	---	Yes	Yes	0,102	---	No	No	0,059	---	No	No
	Quarter 4		0,264	---	Yes	Yes	0,330	---	Yes	Yes	0,382	---	Yes	Yes	0,190	---	No	No	0,152	---	No	No
	Year 2013		0,285	---	Yes	Yes	0,435	---	Yes	Yes	0,453	---	No	Yes	0,037	---	No	No	N/A (product launched in 2013)			
	Year 2014		0,624	---	Yes	Yes	0,859	---	Yes	Yes	0,980	---	No	Yes	0,228	---	No	No	0,188	---	No	No
	Year 2015		0,937	---	Yes	Yes	1,371	---	Yes	Yes	1,452	---	No	Yes	0,449	---	No	No	0,340	---	No	No
Adjusted R^2			0,880				0,653				0,950				0,984				0,987			
ANOVA Sig.			0,000				0,001				0,000				0,000				0,000			

Table 10.46 – Summary of Windmeijer et al (2006) – Market 4 - Liver

Model specification			Windmeijer et al (2006)																	
			Product LI1				Product LI2				Product LI3				Product LI4				Product LI5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			28,366	---	Yes	Yes	16,228	---	Yes	No	18,508	---	Yes	Yes	-2,592	---	No	No	1,649	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,507	No	Yes	Yes	-0,529	No	Yes	Yes	-0,411	No	Yes	Yes	-0,365	No	Yes	Yes	-0,090	No	No	No
	Ln Sales in DDDs lagged two periods		0,031	Yes	No	No	0,013	Yes	No	No	0,008	Yes	No	No	0,127	Yes	No	No	0,336	Yes	Yes	Yes
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	-0,003	No	No	No	0,0004	Yes	No	No	-0,029	No	No	No	0,085	Yes	No	No	0,075	Yes	No	Yes
	Competitive	Ln Competitive marketing expenditures flow	0,029	No	No	No	0,020	No	No	No	0,088	No	No	No	-0,029	Yes	No	No	0,088	No	No	Yes
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	-0,104	No	No	No	0,025	Yes	No	No	0,071	Yes	No	No	0,324	Yes	No	No	0,267	Yes	Yes	Yes
	Competitive	Ln Competitive global marketing expenditures stock	-0,053	Yes	No	No	0,172	No	No	No	0,029	No	No	No	0,031	No	No	No	0,168	No	No	No
Price	Own	Ln Average drug price per DDD	-0,273	Yes	No	No	1,131	No	No	No	-1,055	Yes	No	No	-20,768	Yes	No	No	-1,888	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	0,567	Yes	No	No	0,588	Yes	Yes	Yes	-0,205	No	No	No	-10,242	No	No	No	0,964	Yes	Yes	Yes
Drug age		Drug age	-0,051	No	No	No	0,011	Yes	No	No	-0,002	No	No	No	0,002	Yes	No	No	0,011	Yes	No	No
		Drug age squared	0,0001	No	No	No	-0,0002	Yes	No	No	-0,0001	Yes	No	No	-0,0003	Yes	No	No	-0,0003	Yes	No	Yes
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				0,782	No	No	No	Removed due to multicollinearity			
Temporal dummies		Quarter 2	0,121	---	No	Yes	0,146	---	Yes	Yes	0,108	---	Yes	Yes	0,129	---	Yes	Yes	0,213	---	Yes	Yes
		Quarter 3	0,241	---	Yes	Yes	0,229	---	Yes	Yes	0,213	---	Yes	Yes	0,186	---	Yes	Yes	0,304	---	Yes	Yes
		Quarter 4	0,324	---	Yes	Yes	0,354	---	Yes	Yes	0,278	---	Yes	Yes	0,308	---	Yes	Yes	0,464	---	Yes	Yes
		Year 2013	0,250	---	No	No	0,471	---	Yes	Yes	0,280	---	No	Yes	0,379	---	Yes	Yes	0,627	---	Yes	Yes
		Year 2014	0,706	---	No	Yes	0,917	---	Yes	Yes	0,722	---	Yes	Yes	0,696	---	Yes	Yes	1,150	---	Yes	Yes
		Year 2015	1,077	---	No	Yes	1,317	---	Yes	Yes	1,117	---	Yes	Yes	1,166	---	Yes	Yes	1,621	---	Yes	Yes
Adjusted R^2			0,284				0,578				0,379				0,945				0,755			
ANOVA Sig.			0,046				0,000				0,007				0,000				0,000			

10.4.5.2. Results

Based on the four tables shown above, we prepared a summary of results for a better interpretation, here shown in table 10.47.

Table 10.47 – Summary of Windmeijer et al (2006) (Model 4) results

	Market 1 - Blood (3 products)				Market 2 - Pancreas (5 products)				Market 3 - Heart (5 products)				Leeflang & Wieringa (2010) hyper-tension mean elasti-cities	Market 4 - Liver (5 products)				Leeflang & Wieringa (2010) choles-terol mean elasti-cities	Global (18 products)				Leeflang & Wieringa (2010) model application	
	% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities			% cases with...		Average elasticities			% cases with...		Average elasticities			
	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.		Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.		Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Correct signal and p<0.05	Obtained average elasticity (49 brands)
Ln Sales in DDDs lagged one period	33,3%	0,0%	0,011	0,208	20,0%	0,0%	-0,375	0,020	20,0%	0,0%	-0,287	0,045	-0,0003	0,0%	0,0%	-0,381	N/A	0,020	16,7%	0,0%	-0,288	0,091	16,0%	0,020
Ln Sales in DDDs lagged two periods	100,0%	0,0%	0,151	0,151	20,0%	0,0%	0,005	0,193	80,0%	0,0%	0,085	0,147	0,030	100,0%	20,0%	0,103	0,103	0,050	72,2%	5,6%	0,079	0,134	24,0%	0,050
Ln Global marketing expenditures flow	100,0%	0,0%	0,074	0,074	80,0%	0,0%	0,041	0,041	100,0%	0,0%	0,013	0,013	0,010	60,0%	0,0%	0,026	0,054	0,002	83,3%	0,0%	0,035	0,041	10,0%	0,010
Ln Competitive marketing expenditures flow	0,0%	0,0%	0,057	N/A	40,0%	0,0%	0,055	-0,019	60,0%	0,0%	-0,011	-0,048	0,060	20,0%	0,0%	0,039	-0,029	0,080	33,3%	0,0%	0,033	-0,035	0,0%	0,070
Ln Global marketing expenditures stock	66,7%	0,0%	0,063	0,169	80,0%	0,0%	0,125	0,209	100,0%	20,0%	0,611	0,611	0,100	80,0%	20,0%	0,117	0,172	-0,080	83,3%	11,1%	0,247	0,328	2,0%	-0,070
Ln Competitive global marketing expenditures stock	0,0%	0,0%	0,445	N/A	20,0%	0,0%	0,210	N/A	60,0%	20,0%	-0,008	-0,155	-0,030	20,0%	0,0%	0,069	-0,053	-0,180	27,8%	5,6%	0,150	-0,130	6,0%	-0,050
Ln Average drug price per DDD	66,7%	0,0%	-0,951	-0,951	50,0%	0,0%	4,909	-17,215	40,0%	0,0%	0,082	-2,128	-0,150	80,0%	0,0%	-4,571	-5,996	-0,540	58,8%	0,0%	-2,234	-4,831	10,0%	-0,100
Ln Average competitors drug price per DDD	0,0%	0,0%	-3,925	N/A	40,0%	0,0%	-28,04	-2,957	0,0%	0,0%	-5,506	N/A	-1,150	60,0%	40,0%	-1,666	0,707	1,110	29,4%	11,8%	-10,82	-1,387	10,0%	0,500
Drug age	100,0%	0,0%	0,063	0,063	60,0%	20,0%	0,039	0,070	40,0%	20,0%	0,000	0,052	---	60,0%	0,0%	-0,006	0,008	---	61,1%	11,1%	0,020	0,048	---	---
Drug age squared	100,0%	50,0%	-0,0004	-0,0004	80,0%	60,0%	-0,001	-0,001	66,7%	33,3%	-0,001	-0,0005	---	80,0%	0,0%	-0,0002	-0,0002	---	80,0%	33,3%	-0,0004	-0,0005	---	---
Ln Global marketing expenditures flow x Ln Average drug price per DDD	100,0%	0,0%	0,189	0,189	N/A	N/A	N/A	N/A	50,0%	50,0%	0,041	0,634	-0,080	N/A	N/A	N/A	N/A	-0,270	66,7%	33,3%	0,090	0,411	0,0%	-0,050
Ln Global marketing expenditures flow x Ln Average competitors price per DDD	100,0%	33,3%	-0,113	-0,113	N/A	N/A	N/A	N/A	0,0%	0,0%	0,680	N/A	0,090	0,0%	0,0%	N/A	N/A	-0,130	25,0%	16,7%	0,848	-0,113	8,0%	-0,050
Public reimbursement	66,7%	66,7%	1,742	2,718	---	---	---	---	---	---	---	---	---	---	---	---	---	---	66,7%	66,7%	1,742	2,718	---	---
Loss of exclusivity	---	---	---	---	---	---	---	---	100,0%	---	-0,126	-0,126	---	---	---	---	---	---	100,0%	50,0%	-0,126	-0,126	---	---

Such as performed in the summary table in Model 1, we added comparative data resulting from Leeflang & Wieringa (2010) research using Dutch data. Their data was added to the (comparable) Market 3 – Heart, to the (comparable) Market 4 (Liver), and global results (two last columns).

10.4.6. Comparative analysis of Models 1 to 4

In order to compare the several models fit we calculated, such as performed by Leeflang & Wieringa (2010), the Akaike information criterion (AIC), and the Bayesian information criterion (BIC).

The AIC was proposed by Akaike (1974) and the BIC was proposed by Schwarz (1978), both aiming to help minimize subjective choice of the best model, by quantifying a parameter that can help researchers select the most optimal from multiple alternative models.

The AIC is given by n * Ln(SSR/n) + 2 * k, where:

n = sample size

SSR = sum of squared residuals

k = p + 1

p = number of parameters in the regression

And the BIC is given by n * Ln(SSR/n) + k * Ln(n)

Both criterions penalize models with a higher number of variables, and both are interpreted the same way: the lower the result, the better the model.

The next tables (10.48, 10.49. 10.50, and 10.51) evidence the AICs and BICs for all the products, for each of the four models applied to our data.

Table 10.48 - AICs and BICs for model 1 (Wittink 2002 simplified)

		Model 1 (Wittink 2002 simplified)																	
		Market 1 - Blood			Market 2 - Pancreas					Market 3 - Heart					Market 4 - Liver				
		BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5
	n	48	48	18	48	48	48	33	48	48	48	48	35	48	48	48	48	48	48
	SSR	0,35	0,19	0,01	0,10	0,08	0,07	1,21	0,09	0,09	0,07	0,37	0,18	0,66	0,22	0,12	0,10	0,11	0,18
	k	15	15	13	14	14	14	14	14	14	14	14	13	13	14	14	14	13	14
AIC	AIC	-206,6	-235,6	-107,0	-270,7	-278,1	-286,1	-81,2	-274,1	-271,9	-287,5	-205,8	-159,0	-179,6	-229,6	-259,2	-269,4	-266,3	-238,9	All products
	AIC mean	-183,0			-238,0					-220,8					-252,7					-228,1
	AIC SD	67,5			87,9					56,6					17,5					61,3
BIC	BIC	-178,5	-207,5	-95,4	-244,5	-251,9	-259,9	-60,2	-247,9	-245,7	-261,3	-179,6	-138,8	-155,2	-203,4	-233,0	-243,2	-242,0	-212,7	All products
	BIC mean	-160,5			-212,9					-196,1					-226,8					-203,4
	BIC SD	58,2			85,5					54,6					17,9					58,5

Table 10.49 – AICs and BICs for model 2 (Wittink 2002 complete)

		Model 2 (Wittink 2002 complete)																	
		Market 1 - Blood			Market 2 - Pancreas					Market 3 - Heart					Market 4 - Liver				
		BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5
	n	48	48	18	48	48	48	33	48	48	48	48	35	48	48	48	48	48	48
	SSR	0,33	0,16	0,003	0,08	0,07	0,06	0,94	0,09	0,07	0,05	0,31	0,16	0,66	0,16	0,10	0,09	0,10	0,18
	k	19	19	15	18	18	18	16	18	17	18	16	14	17	18	16	18	17	18
AIC	AIC	-201,2	-236,3	-129,8	-269,2	-275,7	-281,7	-85,6	-267,2	-278,8	-290,6	-210,3	-159,6	-171,5	-238,8	-263,9	-264,2	-260,6	-232,0	All products
	AIC mean	-189,1			-235,9					-222,2					-251,9					-228,7
	AIC SD	54,3			84,2					60,2					15,3					58,2
BIC	BIC	-165,6	-200,8	-116,4	-235,5	-242,0	-248,0	-61,6	-233,5	-247,0	-256,9	-180,4	-137,8	-139,7	-205,1	-233,9	-230,5	-228,8	-198,4	All products
	BIC mean	-160,9			-204,1					-192,4					-219,3					-197,9
	BIC SD	42,4			79,9					57,1					16,4					54,2

Table 10.50 – AICs and BICs for model 3 (Rizzo 1999)

		Model 3 (Rizzo 1999)																	
		Market 1 - Blood			Market 2 - Pancreas					Market 3 - Heart					Market 4 - Liver					
		BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5	
	n	48	48	18	48	48	48	33	48	48	48	48	35	48	48	48	48	48	48	
	SSR	0,39	0,20	0,085	0,11	0,11	0,09	0,71	0,10	0,11	0,12	0,40	0,21	0,16	0,26	0,15	0,14	0,18	0,16	
	k	13	13	9	12	12	12	8	12	11	12	12	12	11	11	11	12	9	12	
AIC	AIC	-205,6	-237,4	-78,5	-267,9	-269,4	-279,8	-110,7	-274,1	-269,5	-263,6	-206,3	-155,1	-250,5	-228,6	-255,7	-257,9	-250,6	-248,9	All products
	AIC mean	-173,8			-240,4					-229,0					-248,4					-228,3
	AIC SD	84,1			72,7					48,2					11,6					57,8
BIC	BIC	-181,3	-213,1	-70,4	-245,4	-247,0	-257,4	-98,7	-251,6	-248,9	-241,1	-183,9	-136,4	-229,9	-208,1	-235,1	-235,4	-233,8	-226,5	All products
	BIC mean	-154,9			-220,0					-208,1					-227,8					-208,0
	BIC SD	74,9			68,0					47,3					11,6					54,4

Table 10.51 – AICs and BICs for model 4 (Windmeijer et al 2006)

		Model 4 (Windmeijer et al 2006)																	
		Market 1 - Blood			Market 2 - Pancreas					Market 3 - Heart					Market 4 - Liver					
		BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5	
	n	48	48	18	48	48	48	33	48	48	48	48	35	48	48	48	48	48	48	
	SSR	0,19	0,16	0,01	0,07	0,05	0,05	0,51	0,07	0,05	0,06	0,18	0,11	0,07	0,17	0,07	0,10	0,07	0,11	
	k	19	18	15	17	17	16	15	17	18	17	19	18	16	17	17	17	18	16	
AIC	AIC	-227,3	-237,4	-98,9	-277,8	-291,5	-298,1	-107,3	-279,3	-297,1	-285,2	-228,9	-164,6	-283,0	-236,8	-278,9	-262,2	-274,9	-259,5	All products
	AIC mean	-187,9			-250,8					-251,8					-262,5					-243,8
	AIC SD	77,2			80,7					55,4					16,5					60,9
BIC	BIC	-191,7	-203,7	-85,6	-246,0	-259,6	-268,1	-84,9	-247,5	-263,4	-253,4	-193,4	-136,6	-253,0	-204,9	-247,1	-230,4	-241,2	-229,5	All products
	BIC mean	-160,3			-221,2					-220,0					-230,6					-213,3
	BIC SD	65,0			76,8					54,2					16,2					57,0

Table 10.52 below summarizes the average AICs and BICs per market.

Table 10.52 – Summary of average AICs and BICs per market and model

		Summary				
		Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Average AIC	Model 1 (Wittink 2002 simplified)	-183,0	-238,0	-220,8	-252,7	-228,1
	Model 2 (Wittink 2002 complete)	-189,1	-235,9	-222,2	-251,9	-228,7
	Model 3 (Rizzo 1999)	-173,8	-240,4	-229,0	-248,4	-228,3
	Model 4 (Winmeijer et al 2006)	-187,9	-250,8	-251,8	-262,5	-243,8

		Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Average BIC	Model 1 (Wittink 2002 simplified)	-160,5	-212,9	-196,1	-226,8	-203,4
	Model 2 (Wittink 2002 complete)	-160,9	-204,1	-192,4	-219,3	-197,9
	Model 3 (Rizzo 1999)	-154,9	-220,0	-208,1	-227,8	-208,0
	Model 4 (Winmeijer et al 2006)	-160,3	-221,2	-220,0	-230,6	-213,3

Source: own elaboration

Figure 10.62 below presents the same information in a chart format.

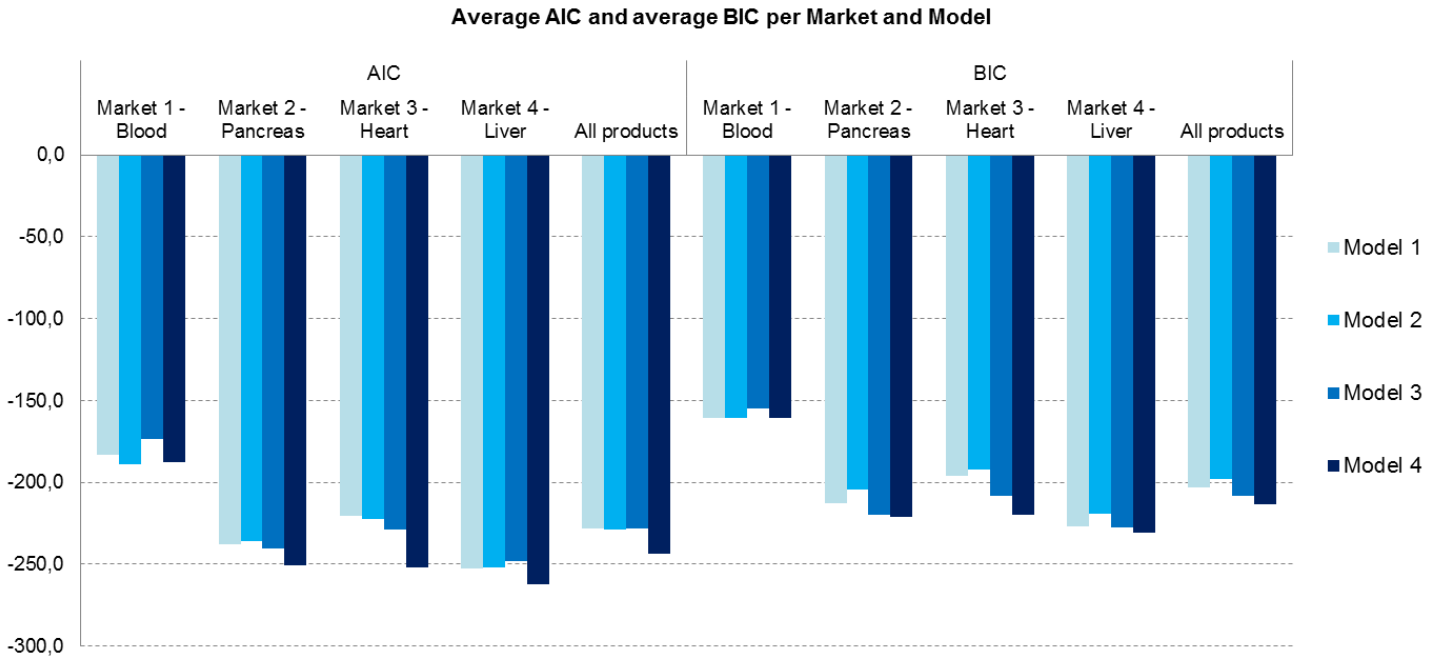


Figure 10.62 – Average AIC and average BIC per Market and Model – graphic

Source: own elaboration

Model 4 – Windmeijer et al (2006) seems to evidence the lower average AICs and BICs. In order to allow additional insights, we calculated the relative likelihood (Burnham & Anderson, 2003) of each model compared with the model with the lower AIC. The formula used was:

exp((AICmin − AICi)/2). As an example, let us compare model 1 against model 4 (the one evidencing the lower average AICs). We get exp ((-228,1 – -243,8)/2) = 0,0004. This means model 1 is 0,0004 times as probable as model 4 to minimize information loss.

Table 10.53 below summarizes these calculations for all markets and models.

Table 10.53 – AIC relative likelihood among markets and models

	Times as probable as model 4 (Windmeijer et al 2006) **to minimize information loss**				
	Market 1 - Blood	**Market 2 - Pancreas**	**Market 3 - Heart**	**Market 4 - Liver**	**All products**
Model 1 (Wittink 2002 simplified)	0,0889	0,0017	0,0000	0,0075	0,0004
Model 2 (Wittink 2002 complete)	1,8395	0,0006	0,0000	0,0051	0,0005
Model 3 (Rizzo 1999)	0,0009	0,0055	0,0000	0,0009	0,0004

Source: own elaboration

Model 4 stands out as the one with the higher fit. We can also interpret AIC values in light of a rule of thumb (Burnham & Anderson, 2004):

- Variation in AIC < 2 → there is substantial evidence for the model, that is, it is not distant to the reference model
- Variation in AIC comprehended between 3 and 7 → there is less support for the model
- Variation in AIC higher than 10 → the model in unlikely to be better than the reference model

Table 10.54 below presents the AIC variation of models 1 to 3 versus model 4.

Table 10.54 – Variation of AIC of models 1 to 3 against model 4

	Variation of AIC of each model versus Model 4 (Windmeijer et al 2006)				
	Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Model 1 (Wittink 2002 simplified)	4,8	12,7	31,0	9,8	15,7
Model 2 (Wittink 2002 complete)	-1,2	14,9	29,6	10,6	15,1
Model 3 (Rizzo 1999)	14,0	10,4	22,8	14,1	15,5

Source: own elaboration

Again, model 4 appears to be the one with the highest fit. The only exception is seen in its the comparison against model 2 in Market 1 (which has a marginally lower average BIC).

Finally, we used a rule of thumb to compare between BICs, using the magnitude of the delta between two BICs, as proposed by Kass & Raftery (1995).

- Variation in BIC less than 2 → the models are not distant (not worth more than a bare mention)

- Variation of BIC comprehended between 2 and 6 → positive evidence against the candidate model

- Variation of BIC comprehended between 6 and 10 → strong evidence against the candidate model

- Variation of BIC greater than 10 → very strong evidence against the candidate model

Table 10.55 highlights the delta of models 1 to 3 BICs against model 4 BICs.

Table 10.55 – Variation of BIC of models 1 to 3 against model 4

	Variation of BIC of each model versus Model 4 (Windmeijer et al 2006)				
	Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Model 1 (Wittink 2002 simplified)	-0,1	8,3	23,8	3,8	10,0
Model 2 (Wittink 2002 complete)	-0,6	17,1	27,6	11,3	15,5
Model 3 (Rizzo 1999)	5,4	1,2	11,9	2,9	5,3

Source: own elaboration

As a conclusion, there is sufficient evidence to consider Model 4 as globally the most suited for the type of data we used. The next step consists of an attempt to build an even better model, based on Model 4, which can better adjust to our data.

10.5. Calibration of Model 4 into three additional models

This chapter describes the procedures and results of the adaptation of Model 4 – Windmeijer et al (2006) to our data, testing three additional models. At the end of this subchapter, we will chose the final model to later assess whether the entry into force of a detailing restriction policy did in fact produce any change in the model parameters, when comparing the before and after of the restriction policy.

10.5.1. Introduction

This sub-chapter describes the main differential characteristics in models 5 to 7, in relation to Model 4.

In **Model 5**, given that our data series has total granularity (non-aggregated comprising a series of promotion investments categories), we adapted Model 4 in the following way:

- Instead of using Ln Global marketing expenditures flow, we used the three variables that more commonly appear in the literature, and one for all other marketing investments (traditional and digital)
    - Ln Detailing flow
    - Ln Mailing flow
    - Ln Journal advertising flow
    - Ln Other marketing expenditures flow

- Instead of using Ln Global marketing expenditures stock, we used:
    - Ln Detailing stock
    - Ln Other marketing expenditures stock

- Instead of the interaction variable Ln Global marketing expenditures flow x Ln Average drug price per DDD, we used ("borrowed" from model 3 - Rizzo, 1999):
    - Average drug price per DDD x Ln Detailing flow
    - Ln Average drug price per DDD x Ln Detailing stock
    - Ln Average drug price per DDD x Drug age

In **Model 6**, we used the original Model 4 and added a series of new variables that, to the extent of our knowledge and except detailing call duration, have not previously been used by the research community studying pharmaceutical marketing. By memory, these variables are shown below in table 10.56.

Table 10.56 – List of additional variables used in Models 6 and 7

	Logarithmized?	Variable name in SPSS	Variable description in SPSS
Visual Aid Type	No	ipad_tablet	% of calls the reps used Ipad / Tablet
	No	laptop	% of calls where the reps used laptop based materials
	No	printed	% of calls where the doctor received printed material
Interest of the contact	No	very_useful	% of calls where doctors considered the information received as very useful
Prescription - future (intention)	No	incr_or_begin	% of calls where doctors declared they would increase or start prescribing the product
Number of products presented	Yes	nr_products	Ln Avg number of products presented during the calls

Source: own elaboration

Finally, in **Model 7**, we used Model 4 with expenditures disaggregation and added the new variables shown above in table 10.56 (by other words, we added the new variables to Model 5). The goal of using these three different models was to use the total combinations of possibilities regarding Model 4, disaggregated expenditures, and new variables, allowing us to control the impact of each decision. Table 10.57 summarizes the variables used in Models 4 to 7.

Table 10.57 – Summary of variables used in models 4 to 7

				New models based on Mode 4		
Model specification			Model 4 (Windmeijer et al, 2006)	Model 5	Model 6	Model 7
Dependent variable			Drug sales in DDDs	Drug sales in DDDs	Drug sales in DDDs	Drug sales in DDDs
Independent variables	Lagged sales		Ln Lagged sales period t-1	Yes	Yes	Yes	Yes
			Ln Lagged sales period t-2	Yes	Yes	Yes	Yes
	Marketing expenditures flow	Own	Ln Detailing flow	No	Yes	No	Yes
			Ln Detailing flow x Ln Detailing flow	No	No	No	No
			Ln Journal advertising flow	No	Yes	No	Yes
			Ln Direct marketing flow	No	Yes	No	Yes
			Ln Global marketing expenditures flow	Yes	No	Yes	No
		Competitive	Ln Competitive detailing flow	No	No	No	No
			Ln Competitive journal advertising flow	No	No	No	No
			Ln Competitive direct marketing flow	No	No	No	No
			Ln Competitive global marketing expenditures flow	Yes	Yes	Yes	Yes
	Marketing expenditures stock	Own	Ln Detailing stock	No	Yes	No	Yes
			Ln Detailing stock x Ln Detailing stock	No	No	No	No
			Ln Global marketing expenditures stock	Yes	No	Yes	No
			Ln Other marketing expenditures stock (except detailing)	No	Yes	No	Yes
		Competitive	Ln Competitive global marketing expenditures stock	Yes	Yes	Yes	Yes
	Price	Own	Ln Average drug price per DDD	Yes	Yes	Yes	Yes
		Competitors	Ln Average competitors drug price per DDD	Yes	Yes	Yes	Yes
	Drug age		Drug age	Yes	Yes	Yes	Yes
			Drug age^2	Yes	Yes	Yes	Yes
			Drug age^3	No	No	No	No
	Marketing expenditures interactions		Average drug price per DDD x Ln Detailing flow	No	Yes	No	Yes
			Ln Average drug price per DDD x Ln Detailing stock	No	Yes	No	Yes
			Ln Average drug price per DDD x Drug age	No	Yes	No	Yes
			Ln Journal advertising flow x Ln Detailing flow	No	No	No	No
			Ln Journal advertising flow x Ln Mailing flow	No	No	No	No
			Ln Mailing flow x Ln Detailing flow	No	No	No	No
			Ln Global marketing expenditures stock x Ln Average drug price per DDD	Yes	No	Yes	No
			Ln Global marketing expenditures stock x Ln Average competitors price per DDD	Yes	Yes	Yes	Yes
	Dummies		Year dummies	Yes	Yes	Yes	Yes
			Month dummies	Yes	Yes	Yes	Yes
			Policy change dummies	Yes	Yes	Yes	Yes
	Other (new variables)		Ipad / Tablet (% of times used in calls)	No	No	Yes	Yes
			Laptop based materials (% of times used in calls)	No	No	Yes	Yes
			Printed material (% of times used in calls)	No	No	Yes	Yes
			Very useful (% of calls)	No	No	Yes	Yes
			Increase / Will begin to prescribe (% of calls)	No	No	Yes	Yes
			Ln Avg number of products presented during the calls	No	No	Yes	Yes

Source: own elaboration

We will now present the results obtained after applying Models 5 to 7.

10.5.2. Model 5 (Model 4 with expenditures disaggregation)

10.5.2.1. Procedures and outputs

Starting with product BL1, SPSS excluded two variables, as seen below (figure 10.63).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	1,521[b]	1,203	,241	,238	4,140E-5
	Drug age	2,276[b]	1,027	,315	,205	1,368E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Year 2013 (dummy), Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Ln Other marketing expenditures stock, Quarter 3 (dummy), Ln Journal advertising flow, Ln Drug price x drug age, Ln Detailing flow (calls), Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures stock x Ln Average competitors price, Public reimbursement (dummy), Ln Detailing stock (calls), Year 2014 (dummy), Ln Sales in DDDs lagged two periods, Ln Average drug price per DDD, Drug age^2, Ln Sales in DDDs lagged one period, Ln Drug price x Ln Detailing flow, Ln Drug price x Ln Detailing stock

Figure 10.63 – Excluded variables for product BL1 in model 5 – iteration 1

Given the experience with Model 4 (very similar to model 5), we removed the interaction variable Ln Global marketing expenditures stock x Ln Average competitors price per DDD (highly correlated with Ln Average competitors price per DDD) and Drug age squared. A second iteration of the regression evidenced another excluded variable: Ln Drug price x Ln Detailing stock (figure 10.64).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing stock	-,266[b]	-,304	,764	-,061	8,852E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Year 2013 (dummy), Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Ln Other marketing expenditures stock, Quarter 3 (dummy), Ln Journal advertising flow, Ln Drug price x drug age, Ln Detailing flow (calls), Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Public reimbursement (dummy), Year 2014 (dummy), Ln Detailing stock (calls), Ln Sales in DDDs lagged two periods, Ln Average drug price per DDD, Ln Sales in DDDs lagged one period, Drug age, Ln Drug price x Ln Detailing flow

Figure 10.64 – Excluded variables for product BL1 in model 5 – iteration 2

The reason for this exclusion was the almost perfect linear combination between the interaction variable and the two individual variables on its basis, which was demonstrated by the outputs below (figure 10.65).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,998[a]	,996	,996	,167371863

a. Predictors: (Constant), Ln Detailing stock (calls), Ln Average drug price per DDD

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	326,872	2	163,436	5834,215	,000[b]
	Residual	1,261	45	,028		
	Total	328,132	47			

a. Dependent Variable: Ln Drug price x Ln Detailing stock

b. Predictors: (Constant), Ln Detailing stock (calls), Ln Average drug price per DDD

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-14,924	1,619		-9,220	,000
	Ln Average drug price per DDD	8,934	,193	1,260	46,388	,000
	Ln Detailing stock (calls)	1,664	,160	,283	10,424	,000

a. Dependent Variable: Ln Drug price x Ln Detailing stock

Figure 10.65 – Linear regression of Ln Drug price x Ln Detailing stock on Ln Average drug price per DDD and Ln Detailing stock, for product BL1 in model 5

We opted to remove the excluded interaction variable, and no additional issues of multicollinearity appeared in product BL1.

Moving to product BL2, SPSS evidenced two excluded variables (figure 10.66):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing stock	1,133[b]	,437	,666	,089	3,164E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	3,227[b]	1,147	,263	,228	2,560E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Ln Journal advertising flow, Year 2014 (dummy), Quarter 2 (dummy), Ln Detailing flow (calls), Year 2013 (dummy), Quarter 3 (dummy), Ln Detailing stock (calls), Ln Other marketing expenditures stock, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Public reimbursement (dummy), Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Average competitors price per DDD, Ln Sales in DDDs lagged one period, Drug age^2, Ln Drug price x drug age, Ln Drug price x Ln Detailing flow, Drug age

Figure 10.66 – Excluded variables for product BL2 in model 5

Given our previous experience with Model 4, we removed these two variables from the independent variables, due to the multicollinearity with the individual base variables. No additional excluded variables resulted after this action.

Regarding product Bl3, we obtained, in a first model iteration, several excluded variables from SPSS (figure 10.67):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000
	Drug age^2	.[b]	.	.	.	,000
	Ln Drug price x Ln Detailing flow	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Public reimbursement (dummy), Ln Detailing flow (calls), Ln Journal advertising flow, Ln Drug price x Ln Detailing stock, Ln Mailing flow, Ln Competitive global marketing expenditures stock, Quarter 3 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Drug price x drug age, Ln Other marketing expenditures stock, Ln Detailing stock (calls)

Figure 10.67 – Excluded variables for product BL3 in model 5 – iteration 1

We started by two variables: removing Ln Drug price x Ln Detailing flow, and Drug age squared. SPSS then excluded the following variables (figure 10.68):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Public reimbursement (dummy), Ln Detailing flow (calls), Ln Journal advertising flow, Ln Drug price x Ln Detailing stock, Ln Mailing flow, Ln Competitive global marketing expenditures stock, Quarter 3 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Drug price x drug age, Ln Other marketing expenditures stock, Ln Detailing stock (calls)

Figure 10.68 – Excluded variables for product BL3 in model 5 – iteration 2

We suspected of the negative effect of the interaction variable Ln Average drug price per DDD x Ln Detailing stock, and removed it. SPSS continued to exclude three variables (figure 10.69):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing stock (calls)	,393[b]	.	.	1,000	6,996E-5
	Ln Average competitors price per DDD	-,359[b]	.	.	-1,000	8,380E-5
	Drug age	2,401[b]	.	.	1,000	1,871E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Public reimbursement (dummy), Ln Detailing flow (calls), Ln Journal advertising flow, Ln Mailing flow, Ln Competitive global marketing expenditures stock, Quarter 3 (dummy), Ln Sales in DDDs lagged one period, Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Drug price x drug age, Ln Other marketing expenditures stock

Figure 10.69 – Excluded variables for product BL3 in model 5 – iteration 3

We then removed the interaction variable Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, resulting in two excluded variables (figure 10.70):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing stock (calls)	,609[b]	.	.	1,000	1,752E-5
	Drug age	,957[b]	.	.	1,000	7,104E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Competitive global marketing expenditures flow, Public reimbursement (dummy), Quarter 2 (dummy), Ln Competitive global marketing expenditures stock, Ln Detailing flow (calls), Ln Journal advertising flow, Ln Mailing flow, Quarter 3 (dummy), Ln Sales in DDDs lagged one period, Ln Other marketing expenditures stock, Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Drug price x drug age, Ln Average competitors price per DDD

Figure 10.70 – Excluded variables for product BL3 in model 5 – iteration 4

We finally removed the variables Ln Drug price per DDD x Drug age, and Ln Detailing stock, in order to eliminate multicollinearity. With this fourth iteration, SPSS did not exclude any more variables.

Moving to product PA1, SPSS excluded two variables (figure 10.71):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing stock	11,296[b]	,594	,558	,118	1,451E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	,807[b]	,101	,920	,020	8,378E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Detailing flow (calls), Year 2014 (dummy), Quarter 3 (dummy), Ln Mailing flow, Quarter 2 (dummy), Year 2013 (dummy), Ln Journal advertising flow, Ln Sales in DDDs lagged one period, Ln Other marketing expenditures stock, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures flow, Ln Detailing stock (calls), Ln Average drug price per DDD, Ln Competitive global marketing expenditures stock, Ln Drug price x drug age, Drug age^2, Ln Drug price x Ln Detailing flow, Ln Average competitors price per DDD, Drug age

Figure 10.71 – Excluded variables for product PA1 in model 5

By removing these interaction variables, no additional multicollinearity issues were found for product PA1.

In the case of product PA2, SPSS excluded three variables (figure 10.72):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	-19,548[b]	-,821	,419	-,159	9,678E-6
	Ln Drug price x Ln Detailing stock	-13,253[b]	-,578	,568	-,113	1,059E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	-48,640[b]	-2,225	,035	-,400	9,901E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Ln Journal advertising flow, Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Quarter 3 (dummy), Ln Average competitors price per DDD, Ln Detailing flow (calls), Ln Competitive global marketing expenditures stock, Ln Detailing stock (calls), Ln Other marketing expenditures stock, Year 2014 (dummy), Ln Drug price x drug age, Drug age^2, Ln Average drug price per DDD, Ln Drug price x Ln Detailing flow

Figure 10.72 – Excluded variables for product PA2 in model 5

We decided to remove the two interaction variables and, given our experience with the data, also Drug age squared (highly correlated with Drug age). After this procedure, no further multicollinearity were detected in the case of product PA2.

In the case of product PA3, SPSS excluded three variables (figure 10.73):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	11,376[b]	1,001	,326	,193	2,710E-5
	Drug age	-15,551[b]	-,729	,473	-,141	7,828E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	-18,032[b]	-1,800	,084	-,333	3,222E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Detailing stock (calls), Ln Detailing flow (calls), Ln Mailing flow, Quarter 2 (dummy), Ln Journal advertising flow, Year 2014 (dummy), Ln Other marketing expenditures stock, Quarter 3 (dummy), Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Drug age^2, Ln Drug price x drug age, Ln Drug price x Ln Detailing flow, Ln Drug price x Ln Detailing stock

Figure 10.73 – Excluded variables for product PA3 in model 5

Given the experience gathered in the previous products using models 4 and 5, we removed the variables Ln Global marketing expenditures stock x Ln Average competitors' price, Drug age squared, and Ln Drug price x Ln Detailing stock, which resulted in no additional excluded variables in SPSS outputs.

In the case of product PA4, we had to remove Ln Average drug price per DDD given that this variable is a constant. We then had to remove all interaction variables involving Ln Average drug price per DDD, to avoid multicollinearity problems. After this procedure, SPSS did not exclude any of the independent variables.

As of product PA5, SPSS excluded two variables (figure 10.74):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	2,235[b]	,113	,911	,023	3,885E-5
	Drug age	-12,925[b]	-,306	,762	-,061	8,444E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Ln Sales in DDDs lagged two periods, Ln Other marketing expenditures stock, Year 2013 (dummy), Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Journal advertising flow, Ln Detailing flow (calls), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Detailing stock (calls), Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Ln Drug price x drug age, Drug age^2, Ln Drug price x Ln Detailing flow, Ln Drug price x Ln Detailing stock, Ln Average drug price per DDD

Figure 10.74 – Excluded variables for product PA5 in model 5 – iteration 1

We decided to remove the variable Drug age squared, and the interaction variable Ln Global marketing expenditures stock x Ln Average competitors price per DDD, decision which resulted in one additional additional excluded variables by SPSS (figure 10.75).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-15,694[b]	-1,258	,220	-,239	9,289E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Ln Sales in DDDs lagged two periods, Ln Other marketing expenditures stock, Year 2013 (dummy), Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Journal advertising flow, Ln Detailing flow (calls), Year 2014 (dummy), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Detailing stock (calls), Ln Average competitors price per DDD, Ln Competitive global marketing expenditures stock, Ln Drug price x drug age, Ln Drug price x Ln Detailing stock, Ln Drug price x Ln Detailing flow, Drug age

Figure 10.75 – Excluded variables for product PA5 in model 5 – iteration 2

We suspected that by removing the interaction variable Ln Drug price x Drug age the issue would be solved, which proved to be a right decision.

Moving to product HE1, SPSS excluded three variables (figure 10.76):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow (calls)	-6,712[b]	-1,173	,251	-,224	7,199E-5
	Ln Detailing stock (calls)	1,507[b]	,105	,917	,021	1,212E-5
	Ln Drug price x drug age	-31,788[b]	-,912	,370	-,176	1,981E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Other marketing expenditures stock, Ln Mailing flow, Ln Journal advertising flow, Quarter 3 (dummy), Year 2013 (dummy), Ln Drug price x Ln Detailing flow, Quarter 2 (dummy), Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Drug price x Ln Detailing stock, Year 2014 (dummy), Ln Average drug price per DDD, Drug age^2, Drug age, Ln Average competitors price per DDD

Figure 10.76 – Excluded variables for product HE1 in model 5

We decided to remove the interaction variables Ln Average drug price per DDD x Ln Detailing flow, Ln Average drug price per DDD x Ln Detailing stock, and Ln Drug price x Drug age, sources of multicollinearity (almost perfect linear relation between the interaction variables and the independent separate variables at their base. No additional excluded variables were excluded by SPSS.

In the case of product HE2, SPSS excluded these two variables (figure 10.77):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-17,062[b]	-1,404	,173	-,270	3,321E-5
	Ln Drug price x drug age	1,635[b]	,129	,899	,026	3,284E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Average competitors price per DDD, Ln Journal advertising flow, Ln Other marketing expenditures stock, Quarter 3 (dummy), Ln Competitive global marketing expenditures stock, Ln Mailing flow, Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures flow, Ln Detailing flow (calls), Year 2014 (dummy), Ln Detailing stock (calls), Ln Drug price x Ln Detailing flow, Drug age^2, Ln Drug price x Ln Detailing stock, Drug age, Ln Global marketing expenditures stock x Ln Average competitors price

Figure 10.77 – Excluded variables for product HE2 in model 5

We removed the interaction variables Ln Drug price x Drug age, and Ln Average drug price per DDD x Ln Detailing stock, resulting in no additional excluded variable.

In the case of product HE3, two variables were removed by SPSS (figure 10.78):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	2,129[b]	,614	,545	,122	6,428E-5
	Ln Drug price x drug age	,161[b]	,019	,985	,004	1,042E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Ln Other marketing expenditures stock, Quarter 3 (dummy), Year 2014 (dummy), Ln Drug price x Ln Detailing flow, Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Year 2013 (dummy), Ln Drug price x Ln Detailing stock, Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Loss of exclusivity (dummy), Ln Sales in DDDs lagged one period, Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Global marketing expenditures stock x Ln Average competitors price, Drug age^2, Ln Detailing flow (calls), Ln Detailing stock (calls)

Figure 10.78 – Excluded variables for product HE3 in model 5

Given our experience with this model and our data, we decided to remove the interaction variable Ln Drug price x Drug age, and the variable Drug age squared, which resulted in no additional excluded variables.

With product HE4, the two excluded variables were the same as in product HE3 (figure 10.79):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	-5,111[b]	-2,077	,048	-,377	5,264E-5
	Ln Drug price x drug age	2,759[b]	,525	,604	,102	1,332E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Average competitors price per DDD, Ln Drug price x Ln Detailing flow, Quarter 3 (dummy), Year 2013 (dummy), Ln Other marketing expenditures stock, Quarter 2 (dummy), Loss of exclusivity (dummy), Ln Drug price x Ln Detailing stock, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Ln Average drug price per DDD, Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Detailing flow (calls), Drug age^2, Ln Detailing stock (calls)

Figure 10.79 – Excluded variables for product HE4 in model 5

We removed the same two variables: the interaction variable Ln Drug price x Drug age, and the variable Drug age squared, resulting in no additional excluded variables due to the issue of multicollinearity.

Regarding product HE5, two variables were excluded due to multicollinearity (figure 10.80):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing stock	-13,419[b]	-1,841	,089	-,455	6,322E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	3,800[b]	1,298	,217	,339	4,373E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Other marketing expenditures stock, Ln Journal advertising flow, Ln Average drug price per DDD, Quarter 2 (dummy), Ln Mailing flow, Ln Detailing flow (calls), Year 2014 (dummy), Ln Average competitors price per DDD, Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Detailing stock (calls), Ln Drug price x drug age, Drug age, Ln Drug price x Ln Detailing flow

Figure 10.80 – Excluded variables for product HE5 in model 5

To solve this issue, we decided to remove these two variables from the regression.

Moving to product LI1, SPSS excluded four variables (figure 10.81):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow (calls)	-1,776[b]	-,111	,912	-,021	6,574E-5
	Ln Detailing stock (calls)	-7,655[b]	-,301	,766	-,058	2,585E-5
	Ln Average competitors price per DDD	-13,383[b]	-,591	,560	-,113	3,220E-5
	Ln Drug price x drug age	31,278[b]	1,188	,245	,223	2,294E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Journal advertising flow, Ln Sales in DDDs lagged two periods, Year 2014 (dummy), Ln Sales in DDDs lagged one period, Ln Mailing flow, Quarter 3 (dummy), Quarter 2 (dummy), Ln Drug price x Ln Detailing flow, Year 2013 (dummy), Ln Drug price x Ln Detailing stock, Ln Competitive global marketing expenditures flow, Ln Other marketing expenditures stock, Ln Competitive global marketing expenditures stock, Ln Average drug price per DDD, Ln Global marketing expenditures stock x Ln Average competitors price, Drug age^2, Drug age

Figure 10.81 – Excluded variables for product LI1 in model 5

Based in our previous experience with this model, we removed the interaction variables Ln Average drug price per DDD x Ln Detailing flow, Ln Average drug price per DDD x Ln Detailing stock, Ln Global marketing expenditures stock x Ln Average competitors price per DDD, and Ln Average drug price per DDD x Drug age, which resulted in no additional problems of multicollinearity.

In the case of product LI2, SPSS excluded three variables (figure 10.82):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	19,934[b]	1,211	,237	,231	3,661E-5
	Drug age	,893[b]	,026	,979	,005	9,058E-6
	Ln Drug price x Ln Detailing stock	-24,659[b]	-1,168	,253	-,223	2,233E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Journal advertising flow, Ln Mailing flow, Ln Other marketing expenditures stock, Quarter 3 (dummy), Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Ln Detailing flow (calls), Ln Sales in DDDs lagged one period, Quarter 2 (dummy), Ln Competitive global marketing expenditures stock, Ln Detailing stock (calls), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Average drug price per DDD, Year 2014 (dummy), Ln Drug price x drug age, Drug age^2, Ln Drug price x Ln Detailing flow

Figure 10.82 – Excluded variables for product LI2 in model 5

By running again the regression without the variables Ln Drug price x Ln Detailing stock, Ln Global marketing expenditures stock x Ln Average competitors price per DDD, and Ln Average drug price per DDD x Drug age, no more multicollinearity issues were detected.

Regarding product LI3, SPSS excluded two variables (figure 10.83):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	-5,706[b]	-,370	,715	-,074	4,412E-5
	Ln Drug price x drug age	-28,278[b]	-1,924	,066	-,359	4,257E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Journal advertising flow, Ln Detailing stock (calls), Ln Drug price x Ln Detailing flow, Ln Other marketing expenditures stock, Quarter 3 (dummy), Ln Sales in DDDs lagged two periods, Year 2013 (dummy), Ln Mailing flow, Ln Sales in DDDs lagged one period, Ln Drug price x Ln Detailing stock, Quarter 2 (dummy), Year 2014 (dummy), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Detailing flow (calls), Drug age, Ln Average drug price per DDD

Figure 10.83 – Excluded variables for product LI3 in model 5

By removing the interaction variables Ln Average drug price per DDD x Drug age and Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, no more issues with multicollinearity were detected.

In the case of product LI4, SPSS excluded three variables (figure 10.84):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow (calls)	-19,155[b]	-,498	,623	-,097	8,602E-7
	Ln Detailing stock (calls)	-13,176[b]	-,134	,894	-,026	1,334E-7
	Ln Drug price x drug age	81,691[b]	,573	,571	,112	6,244E-8

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Journal advertising flow, Year 2014 (dummy), Ln Mailing flow, Quarter 3 (dummy), Year 2013 (dummy), Quarter 2 (dummy), Ln Drug price x Ln Detailing flow, Ln Other marketing expenditures stock, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Competitive global marketing expenditures flow, Ln Drug price x Ln Detailing stock, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Average drug price per DDD, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Average competitors price per DDD, Drug age

Figure 10.84 – Excluded variables for product LI4 in model 5

By removing the interaction variables Ln Average drug price per DDD x Ln Detailing flow, Ln Average drug price per DDD x Ln Detailing stock, and Ln Average drug price per DDD x Drug age, we solved the multicollinearity issues.

Finally, in the case of product LI5, SPSS excluded three variables (figure 10.85):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	6,875[b]	,436	,667	,085	1,985E-5
	Ln Drug price x Ln Detailing stock	14,561[b]	1,201	,241	,229	3,207E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	6,590[b]	,536	,597	,104	3,250E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Mailing flow, Quarter 3 (dummy), Ln Competitive global marketing expenditures stock, Ln Sales in DDDs lagged one period, Year 2013 (dummy), Quarter 2 (dummy), Ln Journal advertising flow, Ln Other marketing expenditures stock, Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Ln Detailing flow (calls), Year 2014 (dummy), Ln Detailing stock (calls), Ln Average drug price per DDD, Ln Average competitors price per DDD, Drug age^2, Ln Drug price x drug age, Ln Drug price x Ln Detailing flow

Figure 10.85 – Excluded variables for product LI5 in model 5

By removing the variables Ln Average drug price per DDD x Ln Detailing stock, Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, and Drug age squared, no mode multicollinearity was detected.

Tables 10.58, 10.59, 10.60 and 10.61 summarize the coefficients obtained in Model 5.

Table 10.58 – Summary of Model 5 – Market 1 - Blood

Model specification			Model 5											
			Product BL1				Product BL2				Product BL3			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			3,303	---	No	No	20,599	---	Yes	Yes	-20,173	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		0,255	Yes	No	No	-0,549	No	Yes	Yes	-0,023	No	No	No
	Ln Sales in DDDs lagged two periods		0,100	Yes	No	No	-0,216	No	No	No	0,166	Yes	No	Yes
Marketing expenditures flow	Own	Ln Detailing flow	-0,070	No	No	No	0,616	Yes	No	Yes	0,022	Yes	No	No
		Ln Journal advertising flow	0,005	Yes	No	No	-0,0002	No	No	No	-0,026	No	No	No
		Ln Direct marketing flow	0,005	Yes	No	No	-0,006	No	No	Yes	0,019	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	0,050	No	No	No	0,077	No	No	No	0,334	No	No	No
Marketing expenditures stock	Own	Ln Detailing stock	0,231	Yes	No	No	0,092	Yes	No	No	Removed due to multicollinearity			
		Ln Other marketing expenditures stock	-0,028	No	No	No	-0,014	No	No	No	-0,303	No	No	No
	Competitive	Ln Competitive global marketing expenditures stock	0,125	No	No	No	0,038	No	No	No	1,653	No	No	No
Price	Own	Ln Average drug price per DDD	-0,290	Yes	No	No	-4,136	Yes	No	No	2,132	No	No	No
	Competitors	Ln Average competitors drug price per DDD	-1,378	No	No	No	-0,246	No	No	No	-4,970	No	No	No
Drug age		Drug age	0,025	Yes	No	No	-0,091	No	No	No	0,048	Yes	No	No
		Drug age squared	Removed due to multicollinearity				-0,001	Yes	Yes	Yes	Removed due to multicollinearity			
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		0,095	Yes	No	No	-0,570	No	No	Yes	Removed due to multicollinearity			
	Ln Average drug price per DDD x Ln Detailing stock		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Average drug price per DDD x Drug age		-0,007	Yes	No	No	0,193	No	Yes	Yes	Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Policy change		Public reimbursement	0,419	Yes	Yes	Yes	-0,182	No	Yes	Yes	6,173	Yes	Yes	Yes
Temporal dummies		Quarter 2	0,039	---	No	No	0,071	---	No	No	-0,029	---	No	No
		Quarter 3	0,111	---	No	No	0,253	---	Yes	Yes	0,091	---	No	No
		Quarter 4	0,226	---	No	No	0,404	---	Yes	Yes	0,196	---	No	No
		Year 2013	0,236	---	No	No	0,463	---	Yes	Yes	N/A (product launched in 2014)			
		Year 2014	0,374	---	No	No	1,228	---	Yes	Yes				
		Year 2015	0,669		No	No	1,617	---	Yes	Yes	0,563	---	No	No
Adjusted R^2			0,997				0,990				1,000			
ANOVA Sig.			0,000				0,000				0,007			

Z

Table 10.59 – Summary of Model 5 – Market 2 - Pancreas

Model specification			Model 5																			
			Product PA1				Product PA2				Product PA3				Product PA4				Product PA5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			30,490	---	Yes	Yes	32,694	---	Yes	Yes	24,767	---	Yes	Yes	59,086	---	No	No	22,091	---	Yes	Yes
Lagged sales	Ln Sales in DDDs lagged one period		-0,577	No	Yes	Yes	-0,554	No	Yes	Yes	-0,588	No	Yes	Yes	-0,127	No	No	No	-0,399	No	Yes	Yes
	Ln Sales in DDDs lagged two periods		-0,061	No	No	No	0,129	Yes	No	No	-0,049	No	No	No	-0,096	No	No	Yes	-0,081	No	No	No
Marketing expenditures flow	Own	Ln Detailing flow	0,087	Yes	No	No	-0,435	No	No	No	0,107	Yes	No	No	0,557	Yes	Yes	Yes	0,115	Yes	No	No
		Ln Journal advertising flow	-0,001	No	No	No	0,006	Yes	Yes	Yes	0,004	Yes	No	No	-0,013	No	No	No	0,001	Yes	No	No
		Ln Direct marketing flow	-0,004	No	No	No	0,002	Yes	No	No	-0,001	No	No	No	0,015	Yes	No	No	-0,002	No	No	No
	Competitive	Ln Competitive marketing expenditures flow	-0,003	Yes	No	No	-0,016	Yes	No	No	0,068	No	No	No	0,034	No	No	No	0,051	No	No	No
Marketing expenditures stock	Own	Ln Detailing stock	0,039	Yes	No	No	-0,240	No	Yes	Yes	0,153	Yes	No	No	3,465	Yes	No	No	-1,054	No	No	No
		Ln Other marketing expenditures stock	0,004	Yes	No	No	0,034	Yes	No	No	0,004	Yes	No	No	0,176	Yes	No	No	-0,019	No	No	No
	Competitive	Ln Competitive global marketing expenditures stock	0,083	No	No	No	0,203	No	No	No	-0,089	Yes	No	No	0,200	No	No	No	0,378	No	No	No
Price	Own	Ln Average drug price per DDD	1,532	No	No	No	-45,601	Yes	Yes	Yes	-8,993	Yes	No	No	Constant (no variation)				-31,802	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	-27,826	No	Yes	Yes	4,479	Yes	No	Yes	1,172	Yes	No	No	-352,29	No	No	No	0,253	Yes	No	No
Drug age		Drug age	-0,081	No	Yes	Yes	-0,098	No	Yes	Yes	-0,121	No	Yes	Yes	0,133	Yes	No	No	-0,006	No	No	No
		Drug age squared	0,0000	Yes	No	No	Removed due to multicollinearity				Removed due to multicollinearity				0,001	No	No	No	Removed due to multicollinearity			
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		-0,275	No	No	No	1,661	Yes	No	No	-0,725	No	No	No	Removed due to multicollinearity				-0,282	No	No	No
	Ln Average drug price per DDD x Ln Detailing stock		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				3,828	Yes	No	No
	Ln Average drug price per DDD x Drug age		0,217	No	Yes	Yes	0,213	No	Yes	Yes	0,350	No	Yes	Yes	Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				-7,236	Yes	No	No	Removed due to multicollinearity			
Temporal dummies		Quarter 2	0,128	---	Yes	Yes	0,121	---	Yes	Yes	0,148	---	Yes	Yes	-0,041	---	No	No	0,032	---	No	No
		Quarter 3	0,233	---	Yes	Yes	0,288	---	Yes	Yes	0,236	---	Yes	Yes	0,353	---	No	No	0,101	---	No	No
		Quarter 4	0,352	---	Yes	Yes	0,414	---	Yes	Yes	0,328	---	Yes	Yes	0,240	---	No	No	0,138	---	No	No
		Year 2013	0,310	---	Yes	Yes	0,404	---	Yes	Yes	0,366	---	Yes	Yes	N/A (product launched in 2013)				0,087	---	No	No
		Year 2014	-0,014	---	No	No	0,299	---	No	No	0,848	---	Yes	Yes	-0,140	---	No	No	0,065	---	No	No
		Year 2015	0,310	---	No	No	0,727	---	No	Yes	1,283	---	Yes	Yes	0,061	---	No	No	0,235	---	No	No
Adjusted R^2			0,760				0,752				0,837				0,964				0,335			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,030			

Table 10.60 – Summary of Model 5 – Market 3 - Heart

Model specification			Model 5																			
			Product HE1				Product HE2				Product HE3				Product HE4				Product HE5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			26,793	---	Yes	Yes	23,036	---	Yes	Yes	5,066	---	No	No	22,341	---	Yes	Yes	-2,654	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,801	No	Yes	Yes	-0,470	No	Yes	Yes	-0,080	No	No	No	-0,065	No	No	No	-0,004	No	No	No
	Ln Sales in DDDs lagged two periods		-0,245	No	No	No	0,151	Yes	No	No	0,806	Yes	Yes	Yes	0,187	Yes	No	No	0,013	Yes	No	No
Marketing expenditures flow	Own	Ln Detailing flow	0,027	Yes	No	No	0,054	Yes	No	No	-0,071	No	No	No	0,202	Yes	No	Yes	0,456	Yes	No	No
		Ln Journal advertising flow	-0,002	No	No	No	0,006	Yes	Yes	Yes	No investments in time series				No investments in time series				0,001	Yes	No	No
		Ln Direct marketing flow	-0,008	No	No	Yes	-0,007	No	Yes	Yes	0,002	Yes	No	No	No investments in time series				-0,001	No	No	No
	Competitive	Ln Competitive marketing expenditures flow	-0,070	Yes	Yes	Yes	-0,047	Yes	No	No	0,063	No	No	No	-0,041	Yes	No	No	0,019	No	No	No
Marketing expenditures stock	Own	Ln Detailing stock	0,424	Yes	No	No	-0,294	No	No	No	0,548	Yes	No	No	0,745	Yes	No	Yes	0,183	Yes	No	No
		Ln Other marketing expenditures stock	0,015	Yes	No	No	0,022	Yes	No	No	0,028	Yes	Yes	Yes	0,004	Yes	No	No	0,006	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	0,023	No	No	No	-0,049	Yes	No	No	0,142	No	No	No	-0,384	Yes	Yes	Yes	0,305	No	No	No
Price	Own	Ln Average drug price per DDD	1,266	No	No	No	0,562	No	No	No	1,330	No	No	No	-1,595	Yes	No	No	-5,833	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	-3,716	No	No	No	3,290	Yes	No	No	-12,219	No	Yes	Yes	-1,931	No	No	Yes	-1,713	No	No	No
Drug age		Drug age	0,025	Yes	No	No	-0,003	No	No	No	-0,064	No	Yes	Yes	-0,048	No	Yes	Yes	0,146	Yes	Yes	Yes
		Drug age squared	-0,0002	Yes	No	Yes	0,000	Yes	Yes	Yes	Removed due to multicollinearity				Removed due to multicollinearity				-0,001	Yes	No	No
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		Removed due to multicollinearity				0,038	Yes	No	No	-0,047	No	No	No	0,153	Yes	No	Yes	0,409	Yes	No	No
	Ln Average drug price per DDD x Ln Detailing stock		Removed due to multicollinearity				Removed due to multicollinearity				-0,067	No	No	No	0,523	Yes	No	Yes	Removed due to multicollinearity			
	Ln Average drug price per DDD x Drug age		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				0,064	No	No	No
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		0,301	No	No	No	-0,271	Yes	No	No	0,781	No	Yes	Yes	0,063	No	No	No	Removed due to multicollinearity			
Policy change	Loss of exclusivity		N/A				N/A				-0,120	Yes	No	No	-0,166	Yes	Yes	Yes	N/A			
Temporal dummies	Quarter 2		0,088	---	Yes	Yes	0,155	---	Yes	Yes	0,154	---	Yes	Yes	0,082	---	No	No	0,037	---	No	No
	Quarter 3		0,160	---	Yes	Yes	0,233	---	Yes	Yes	0,200	---	Yes	Yes	0,138	---	No	No	0,033	---	No	No
	Quarter 4		0,239	---	Yes	Yes	0,391	---	Yes	Yes	0,462	---	Yes	Yes	0,266	---	Yes	Yes	0,129	---	No	No
	Year 2013		0,264	---	Yes	Yes	0,465	---	Yes	Yes	0,827	---	Yes	Yes	0,152	---	No	No	N/A (product launched in 2013)			
	Year 2014		0,618	---	Yes	Yes	1,025	---	Yes	Yes	1,551	---	Yes	Yes	0,433	---	No	No	0,161	---	No	No
	Year 2015		0,927	---	Yes	Yes	1,717	---	Yes	Yes	2,093	---	Yes	Yes	0,728	---	No	No	0,266	---	No	No
Adjusted R^2			0,887				0,757				0,962				0,984				0,987			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,000			

Table 10.61 – Summary of Model 5 – Market 4 - Liver

Model specification			Model 5																	
			Product LI1				Product LI2				Product LI3				Product LI4				Product LI5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			30,790	---	Yes	Yes	13,538	---	No	Yes	12,034	---	No	No	-1,424	---	No	No	9,203	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,540	No	Yes	Yes	-0,581	No	Yes	Yes	-0,449	No	Yes	Yes	-0,442	No	Yes	Yes	-0,102	No	No	No
	Ln Sales in DDDs lagged two periods		-0,020	No	No	No	-0,059	No	No	No	0,035	No	No	No	0,060	Yes	No	No	0,294	Yes	No	No
Marketing expenditures flow	Own	Ln Detailing flow	-0,029	No	No	No	0,576	Yes	No	No	0,761	Yes	No	No	0,030	Yes	No	No	-0,328	No	No	No
		Ln Journal advertising flow	0,003	Yes	No	No	-0,001	No	No	No	0,007	Yes	Yes	Yes	-0,002	No	No	No	0,001	Yes	No	No
		Ln Direct marketing flow	-0,002	No	No	No	-0,002	Yes	No	No	0,004	Yes	No	No	0,001	Yes	No	No	-0,008	No	No	Yes
	Competitive	Ln Competitive marketing expenditures flow	0,027	No	No	No	0,029	No	No	No	0,076	No	No	No	-0,032	Yes	No	No	0,082	No	No	Yes
Marketing expenditures stock	Own	Ln Detailing stock	-0,125	No	No	No	0,048	Yes	No	No	0,256	Yes	No	No	-0,121	No	No	No	0,257	Yes	No	Yes
		Ln Other marketing expenditures stock	0,018	Yes	No	No	-0,013	No	No	No	0,037	Yes	No	Yes	0,027	Yes	No	No	0,009	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	-0,059	Yes	No	No	0,154	No	No	No	-0,083	Yes	No	No	0,044	No	No	No	0,188	No	No	No
Price	Own	Ln Average drug price per DDD	-1,031	Yes	No	No	8,206	No	No	No	-12,130	Yes	No	No	-30,522	Yes	No	No	-9,496	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	0,762	Yes	No	No	0,622	Yes	Yes	Yes	-0,445	No	No	No	6,519	Yes	No	No	0,985	Yes	Yes	Yes
Drug age		Drug age	-0,080	No	No	No	0,007	Yes	No	No	0,038	Yes	No	No	0,002	Yes	No	No	-0,083	No	No	Yes
		Drug age squared	0,0002	No	No	No	-0,0001	Yes	No	No	-0,0003	Yes	Yes	Yes	-0,0002	Yes	No	No	Removed due to multicollinearity			
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		Removed due to multicollinearity				-0,893	No	No	No	1,534	Yes	No	No	Removed due to multicollinearity				0,594	Yes	No	No
	Ln Average drug price per DDD x Ln Detailing stock		Removed due to multicollinearity				Removed due to multicollinearity				0,262	Yes	No	No	Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Average drug price per DDD x Drug age		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				0,106	No	No	Yes
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				-0,516	Yes	No	No	Removed due to multicollinearity			
Temporal dummies		Quarter 2	0,107	---	No	No	0,143	---	Yes	Yes	0,102	---	Yes	Yes	0,133	---	Yes	Yes	0,174	---	Yes	Yes
		Quarter 3	0,235	---	Yes	Yes	0,219	---	Yes	Yes	0,215	---	Yes	Yes	0,169	---	Yes	Yes	0,262	---	Yes	Yes
		Quarter 4	0,314	---	No	Yes	0,334	---	Yes	Yes	0,295	---	Yes	Yes	0,298	---	Yes	Yes	0,403	---	Yes	Yes
		Year 2013	0,246	---	No	No	0,458	---	Yes	Yes	0,274	---	No	Yes	0,382	---	Yes	Yes	0,499	---	Yes	Yes
		Year 2014	0,686	---	No	No	0,873	---	Yes	Yes	0,704	---	Yes	Yes	0,717	---	Yes	Yes	0,948	---	Yes	Yes
		Year 2015	1,022	---	No	No	1,243	---	Yes	Yes	1,143	---	Yes	Yes	1,141	---	Yes	Yes	1,351	---	Yes	Yes
Adjusted R^2			0,241				0,534				0,523				0,942				0,766			
ANOVA Sig.			0,080				0,001				0,002				0,000				0,000			

10.5.2.2. Results

Based on the four tables shown above, we prepared a summary of results for a better interpretation, shown in table 10.62.

Table 10.62 – Summary of Model 5 results

	Market 1 - Blood (3 products)				Market 2 - Pancreas (5 products)				Market 3 - Heart (5 products)				Market 4 - Liver (5 products)				Global (18 products)			
	% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities	
	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.
Ln Sales in DDDs lagged one period	33,3%	0,0%	-0,106	0,255	0,0%	0,0%	-0,449	N/A	0,0%	0,0%	-0,284	N/A	0,0%	0,0%	-0,423	N/A	5,6%	0,0%	-0,339	0,255
Ln Sales in DDDs lagged two periods	66,7%	0,0%	0,017	0,133	20,0%	0,0%	-0,032	0,129	80,0%	20,0%	0,182	0,289	40,0%	0,0%	0,062	0,130	50,0%	5,6%	0,062	0,194
Ln Detailing flow	66,7%	0,0%	0,189	0,319	80,0%	20,0%	0,086	0,216	80,0%	0,0%	0,134	0,185	60,0%	0,0%	0,202	0,456	72,2%	5,6%	0,149	0,278
Ln Journal advertising flow	33,3%	0,0%	-0,007	0,005	60,0%	20,0%	-0,001	0,004	66,7%	33,3%	0,002	0,003	60,0%	20,0%	0,002	0,004	56,3%	18,8%	-0,001	0,004
Ln Direct marketing flow	66,7%	0,0%	0,006	0,012	40,0%	0,0%	0,002	0,008	25,0%	0,0%	-0,004	0,002	60,0%	0,0%	-0,002	0,002	47,1%	0,0%	0,0003	0,007
Ln Competitive marketing expenditures flow	0,0%	0,0%	0,153	N/A	40,0%	0,0%	0,027	-0,010	60,0%	20,0%	-0,015	-0,053	20,0%	0,0%	0,037	-0,032	33,3%	5,6%	0,039	-0,035
Ln Detailing stock	100,0%	0,0%	0,162	0,162	60,0%	0,0%	0,473	1,219	80,0%	0,0%	0,321	0,475	60,0%	0,0%	0,063	0,187	70,6%	0,0%	0,271	0,537
Ln Other marketing expenditures stock	0,0%	0,0%	-0,115	N/A	80,0%	0,0%	0,040	0,055	100,0%	20,0%	0,015	0,015	80,0%	0,0%	0,016	0,023	72,2%	5,6%	0,0004	0,030
Ln Competitive global marketing expenditures stock	0,0%	0,0%	0,605	N/A	20,0%	0,0%	0,155	-0,089	40,0%	20,0%	0,007	-0,217	40,0%	0,0%	0,049	-0,071	27,8%	5,6%	0,160	-0,133
Ln Average drug price per DDD	66,7%	0,0%	-0,765	-2,213	75,0%	25,0%	-21,22	-28,799	40,0%	0,0%	-0,854	-3,714	80,0%	0,0%	-8,994	-13,295	64,7%	5,9%	-8,024	-13,766
Ln Average competitors drug price per DDD	0,0%	0,0%	-2,198	N/A	60,0%	0,0%	-74,84	1,97	20,0%	0,0%	-3,257	3,290	80,0%	40,0%	1,689	2,222	44,4%	11,1%	-21,59	2,202
Drug age	66,7%	0,0%	-0,006	0,036	20,0%	0,0%	-0,035	0,133	40,0%	20,0%	0,011	0,085	60,0%	0,0%	-0,023	0,016	44,4%	5,6%	-0,014	0,053
Drug age squared	100,0%	100,0%	-0,0007	-0,0007	50,0%	0,0%	0,0004	-0,00002	100,0%	33,3%	-0,0004	-0,0004	75,0%	25,0%	-0,0001	-0,0002	80,0%	30,0%	-0,0002	-0,0003
Ln Average drug price per DDD x Ln Detailing flow	50,0%	0,0%	-0,238	0,095	25,0%	0,0%	0,076	1,661	75,0%	0,0%	0,138	0,200	66,7%	0,0%	0,412	1,064	53,8%	0,0%	0,130	0,640
Ln Average drug price per DDD x Ln Detailing stock	N/A	N/A	N/A	N/A	100,0%	0,0%	3,828	3,828	50,0%	0,0%	0,228	0,523	100,0%	0,0%	0,262	0,262	75,0%	0,0%	1,137	1,538
Ln Average drug price per DDD x Drug age	50,0%	0,0%	0,093	-0,007	0,0%	0,0%	0,260	N/A	0,0%	0,0%	0,064	N/A	0,0%	0,0%	0,106	N/A	14,3%	0,0%	0,162	-0,007
Ln Global marketing expenditures stock x Ln	N/A	N/A	N/A	N/A	100,0%	0,0%	-7,236	-7,236	25,0%	0,0%	0,218	-0,271	100,0%	0,0%	-0,516	-0,516	50,0%	0,0%	-1,147	-2,674
Public reimbursement	66,7%	66,7%	2,137	3,296	---	---	---	---	---	---	---	---	---	---	---	---	66,7%	66,7%	2,137	3,296
Loss of exclusivity	---	---	---	---	---	---	---	---	100,0%	50,0%	-0,143	-0,143	---	---	---	---	100,0%	50,0%	-0,143	-0,143

10.5.3. Model 6 (original Model 4 + new variables)

10.5.3.1. Procedures and outputs

Starting with product BL1, SPSS excluded two variables, as seen below (figure 10.86).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	,557[b]	,412	,684	,086	4,032E-5
	Ln Average competitors price per DDD	-,639[b]	-,547	,589	-,113	5,394E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 2 (dummy), Year 2013 (dummy), Printed material (% of times used in calls), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Very useful (% of calls), Laptop based materials (% of times used in calls), Ln Competitive global marketing expenditures stock, Quarter 4 (dummy), Increase / Will begin to prescribe (% of calls), Year 2014 (dummy), Ipad / Tablet (% of times used in calls), Ln Global marketing expenditures flow, Ln Avg number of products presented during the calls, Ln Global marketing expenditures stock, Public reimbursement (dummy), Drug age^2, Ln Global marketing expenditures stock x Ln Average drug price, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Year 2015 (dummy), Drug age

Figure 10.86 – Excluded variables for product BL1 in model 6

Given the experience with Model 4, we removed the interaction variables Ln Global marketing expenditures stock x Ln Average drug price per DDD and Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, which solved the multicollinearity issues.

In the case of product BL2, also two variables were removed by SPSS, as shown below (figure 10.87).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	3,699[b]	,846	,406	,174	1,532E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	5,684[b]	1,358	,188	,272	1,595E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Avg number of products presented during the calls, Ln Global marketing expenditures flow, Quarter 2 (dummy), Very useful (% of calls), Laptop based materials (% of times used in calls), Ipad / Tablet (% of times used in calls), Year 2013 (dummy), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Public reimbursement (dummy), Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Ln Average drug price per DDD, Ln Average competitors price per DDD, Ln Sales in DDDs lagged two periods, Drug age^2, Drug age

Figure 10.87 – Excluded variables for product BL2 in model 6

We removed these two variables from the regression (the same two removed in the case of product BL1).

A more delicate case was noticed with product BL3. SPSS excluded several variables (figure 10.88):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Sales in DDDs lagged two periods	.[b]	.	.	.	,000
	Ln Global marketing expenditures stock	.[b]	.	.	.	,000
	Ln Average drug price per DDD	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000
	Drug age^2	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ipad / Tablet (% of times used in calls), Ln Global marketing expenditures stock x Ln Average drug price, Ln Competitive global marketing expenditures stock, Laptop based materials (% of times used in calls), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Quarter 3 (dummy), Ln Sales in DDDs lagged one period, Ln Avg number of products presented during the calls, Ln Global marketing expenditures flow, Increase / Will begin to prescribe (% of calls), Very useful (% of calls), Printed material (% of times used in calls), Public reimbursement (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 4 (dummy)

Figure 10.88 – Excluded variables for product BL3 in model 6 – iteration 1

As with products BL1 and BL2, we removed the two interaction variables Ln Global marketing expenditures stock x Ln Average drug price per DDD and Ln Global marketing expenditures stock x Ln Average competitors' price per DDD). We also removed the variable Drug age squared, and ran the regression again. Excluded variables are shown below in figure 10.89.

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ipad / Tablet (% of times used in calls), Quarter 4 (dummy), Quarter 2 (dummy), Laptop based materials (% of times used in calls), Ln Competitive global marketing expenditures stock, Public reimbursement (dummy), Increase / Will begin to prescribe (% of calls), Ln Avg number of products presented during the calls, Ln Global marketing expenditures flow, Ln Competitive global marketing expenditures flow, Printed material (% of times used in calls), Very useful (% of calls), Ln Sales in DDDs lagged two periods, Ln Average drug price per DDD, Ln Sales in DDDs lagged one period, Quarter 3 (dummy)

Figure 10.89 – Excluded variables for product BL3 in model 6 – iteration 2

We then decided to remove the variable Ln Global marketing expenditures stock, given that it an almost perfect combination of the two lagged sales variables (figure 10.90).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,977[a]	,955	,949	,129122201

a. Predictors: (Constant), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	5,322	2	2,661	159,606	,000[b]
	Residual	,250	15	,017		
	Total	5,572	17			

a. Dependent Variable: Ln Global marketing expenditures stock

b. Predictors: (Constant), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	11,118	,118		94,236	,000
	Ln Sales in DDDs lagged one period	,084	,028	,485	3,048	,008
	Ln Sales in DDDs lagged two periods	,071	,022	,508	3,191	,006

a. Dependent Variable: Ln Global marketing expenditures stock

Figure 10.90 – Regression of Ln Global marketing expenditures stock on Ln Sales in DDD lagged on period and Ln Sales in DDDs lagged two periods, for product BL3 in model 6

This new iteration provoked two excluded variables in SPSS outputs (figure 10.91):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ipad / Tablet (% of times used in calls), Quarter 4 (dummy), Quarter 2 (dummy), Laptop based materials (% of times used in calls), Ln Competitive global marketing expenditures stock, Public reimbursement (dummy), Increase / Will begin to prescribe (% of calls), Ln Avg number of products presented during the calls, Ln Global marketing expenditures flow, Ln Competitive global marketing expenditures flow, Printed material (% of times used in calls), Very useful (% of calls), Ln Sales in DDDs lagged two periods, Ln Average drug price per DDD, Ln Sales in DDDs lagged one period, Quarter 3 (dummy)

Figure 10.91 – Excluded variables for product BL3 in model 6 – iteration 3

We then removed the variable Ln Average competitors price per DDD, which is highly correlated with Drug age (adjusted R^2 = 0,825), which resulted in no additional multicollinearity issues. However, the resulting R^2 is equal to one, and the p-values (sig. columns in the coefficients output) has missing values.

Moving to product PA1, SPSS excluded two variables (figure 10.92), which we removed to solve the multicollinearity issues (the exact same situation as with products BL1 and BL2):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	4,368[b]	,122	,904	,025	5,653E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	13,097[b]	,390	,700	,079	6,379E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Laptop based materials (% of times used in calls), Ln Avg number of products presented during the calls, Very useful (% of calls), Year 2013 (dummy), Quarter 3 (dummy), Ln Global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Increase / Will begin to prescribe (% of calls), Ln Sales in DDDs lagged one period, Quarter 2 (dummy), Ln Global marketing expenditures stock, Ln Sales in DDDs lagged two periods, Ln Average drug price per DDD, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Drug age, Ln Average competitors price per DDD

Figure 10.92 – Excluded variables for product PA1 in model 6

With product PA2, we applied the same procedure as with products BL1, BL2 and PA1, in order to remove the multicollinearity provoked by the interaction variables below (figure 10.93):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	-20,779[b]	-,549	,588	-,111	5,456E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	-21,142[b]	-,616	,544	-,125	6,600E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Increase / Will begin to prescribe (% of calls), Printed material (% of times used in calls), Laptop based materials (% of times used in calls), Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Very useful (% of calls), Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Quarter 3 (dummy), Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures flow, Ln Average competitors price per DDD, Ln Global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Ln Average drug price per DDD, Drug age

Figure 10.93 – Excluded variables for product PA2 in model 6

The same with product PA3 (figure 10.94):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	-13,050[b]	-,976	,339	-,195	2,047E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	-13,778[b]	-1,096	,284	-,218	2,295E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Increase / Will begin to prescribe (% of calls), Ln Global marketing expenditures stock, Ln Global marketing expenditures flow, Laptop based materials (% of times used in calls), Very useful (% of calls), Ln Avg number of products presented during the calls, Ipad / Tablet (% of times used in calls), Quarter 3 (dummy), Year 2013 (dummy), Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures flow, Ln Average competitors price per DDD, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Ln Average drug price per DDD, Drug age

Figure 10.94 – Excluded variables for product PA3 in model 6

In the case of product PA4, SPSS excluded two variables (figure 10.95):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	-51,376[b]	-,980	,348	-,283	4,395E-7
	Ln Global marketing expenditures stock x Ln Average drug price	-51,213[b]	-,975	,351	-,282	4,380E-7

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Laptop based materials (% of times used in calls), Quarter 3 (dummy), Very useful (% of calls), Printed material (% of times used in calls), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 4 (dummy), Ln Competitive global marketing expenditures flow, Ln Avg number of products presented during the calls, Quarter 2 (dummy), Increase / Will begin to prescribe (% of calls), Ln Global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Year 2014 (dummy), Drug age^2, Drug age

Figure 10.95 – Excluded variables for product PA4 in model 6

By removing the two interaction variables that had shown before to provoke problems (Ln Global marketing expenditures stock x Ln Average drug price per DDD and Ln Global marketing expenditures stock x Ln Average competitors price per DDD), we solved the multicollinearity issues.

Moving to product PA4, SPSS removed two variables (figure 10.96):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-22,357[b]	-1,265	,218	-,250	5,254E-5
	Ln Average competitors price per DDD	-35,849[b]	-2,020	,055	-,381	4,753E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged two periods, Laptop based materials (% of times used in calls), Printed material (% of times used in calls), Very useful (% of calls), Year 2013 (dummy), Increase / Will begin to prescribe (% of calls), Ln Avg number of products presented during the calls, Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 3 (dummy), Ln Global marketing expenditures stock, Ln Competitive global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Ln Global marketing expenditures stock x Ln Average drug price, Drug age

Figure 10.96 – Excluded variables for product PA5 in model 6

By applying the same treatment as the previous product (revoving the interaction variables), we solved the multicollinearity issues.

With product HE1, SPSS excluded one variable only (figure 10.97):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	8,656[b]	,567	,576	,117	1,231E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Increase / Will begin to prescribe (% of calls), Printed material (% of times used in calls), Quarter 3 (dummy), Laptop based materials (% of times used in calls), Ln Avg number of products presented during the calls, Year 2013 (dummy), Ln Competitive global marketing expenditures stock, Very useful (% of calls), Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average drug price, Ipad / Tablet (% of times used in calls), Ln Global marketing expenditures stock x Ln Average competitors price, Ln Global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Year 2014 (dummy), Ln Average drug price per DDD, Drug age^2, Drug age, Ln Average competitors price per DDD

Figure 10.97 – Excluded variables for product HE1 in model 6

We applied the same "treatment" as in all other products analyzed so far, removing the two interaction variables provoking the multicollinearity issues.

In the case of product HE2, SPSS excluded two variables (figure 10.98):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	11,013[b]	,574	,572	,116	2,238E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	11,169[b]	,997	,329	,199	6,400E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Avg number of products presented during the calls, Ln Competitive global marketing expenditures flow, Very useful (% of calls), Quarter 2 (dummy), Year 2014 (dummy), Laptop based materials (% of times used in calls), Increase / Will begin to prescribe (% of calls), Ln Sales in DDDs lagged one period, Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged two periods, Quarter 3 (dummy), Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Global marketing expenditures stock, Ln Global marketing expenditures stock x Ln Average drug price, Drug age^2, Drug age

Figure 10.98 – Excluded variables for product HE2 in model 6

We suspected that the origin of the multicollinearity was the inclusion of the two interaction variables. By removing them from the list of independent variables, no more issues were detected.

Moving to product HE3, SPSS excluded two variables (figure 10.99):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age^2	-73,354[b]	-3,744	,010	-,837	6,621E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	14,391[b]	1,885	,108	,610	9,139E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Global marketing expenditures flow, Very useful (% of calls), Year 2014 (dummy), Ln Competitive global marketing expenditures flow, Quarter 4 (dummy), Printed material (% of times used in calls), Quarter 2 (dummy), Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Ln Competitive global marketing expenditures stock, Year 2013 (dummy), Quarter 3 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Increase / Will begin to prescribe (% of calls), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Average competitors price per DDD, Ln Global marketing expenditures stock, Drug age, Ln Average drug price per DDD

Figure 10.99 – Excluded variables for product HE3 in model 6

We removed these two variables from the regression, in order to solve the multicollinearity issues.

In the case of product HE4, we noted that the dataset has very limited information available regarding the new variables. Therefore, we removed those variables, and as a consequence product HE4 in Model 6 will have the same outputs as in Model 4.

Regarding product HE5, SPSS excluded two variables (figure 10.100):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	-8,904[b]	-2,218	,047	-,539	1,312E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	11,893[b]	1,041	,318	,288	2,097E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Global marketing expenditures stock, Ln Average drug price per DDD, Quarter 3 (dummy), Ipad / Tablet (% of times used in calls), Laptop based materials (% of times used in calls), Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Ln Global marketing expenditures flow, Ln Average competitors price per DDD, Year 2014 (dummy), Quarter 2 (dummy), Very useful (% of calls), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Sales in DDDs lagged one period, Drug age

Figure 10.100 – Excluded variables for product HE5 in model 6

By removing these two interaction variables, no more multicollinearity issues were detected.

Moving to product LI1, SPSS excluded two variables due to multicollinearity (figure 10.101):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	10,764[b]	,360	,722	,073	1,990E-5
	Ln Average competitors price per DDD	-18,194[b]	-,708	,486	-,143	2,645E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Avg number of products presented during the calls, Very useful (% of calls), Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged two periods, Year 2014 (dummy), Ln Global marketing expenditures stock x Ln Average drug price, Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Printed material (% of times used in calls), Quarter 3 (dummy), Increase / Will begin to prescribe (% of calls), Ln Competitive global marketing expenditures flow, Laptop based materials (% of times used in calls), Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Global marketing expenditures stock, Drug age^2, Drug age

Figure 10.101 – Excluded variables for product LI1 in model 6

This problem was solved by removing the two interaction variables from the regression model.

A similar situation occurred with product LI2 (figure 10.102):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	13,239[b]	,876	,390	,176	4,435E-5
	Ln Global marketing expenditures stock x Ln Average drug price	-18,849[b]	-,871	,392	-,175	2,161E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Laptop based materials (% of times used in calls), Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Printed material (% of times used in calls), Quarter 3 (dummy), Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Very useful (% of calls), Ln Global marketing expenditures stock, Ln Sales in DDDs lagged one period, Quarter 2 (dummy), Ln Competitive global marketing expenditures stock, Ln Global marketing expenditures flow, Ln Competitive global marketing expenditures flow, Increase / Will begin to prescribe (% of calls), Year 2014 (dummy), Ln Average drug price per DDD, Ln Global marketing expenditures stock x Ln Average competitors price, Drug age^2, Drug age

Figure 10.102 – Excluded variables for product LI2 in model 6

After removing the interaction variables, the multicollinearity issues were solved.

In the case of product LI3, SPSS excluded two variables due to the multicollinearity with the two interaction variables (figure 10.103):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-,191[b]	-,012	,990	-,003	5,390E-5
	Ln Average competitors price per DDD	-12,902[b]	-,804	,429	-,162	4,856E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Global marketing expenditures stock, Laptop based materials (% of times used in calls), Very useful (% of calls), Quarter 3 (dummy), Ln Global marketing expenditures flow, Ln Sales in DDDs lagged two periods, Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged one period, Ln Avg number of products presented during the calls, Quarter 2 (dummy), Year 2013 (dummy), Increase / Will begin to prescribe (% of calls), Ln Global marketing expenditures stock x Ln Average drug price, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Competitive global marketing expenditures flow, Year 2014 (dummy), Ln Competitive global marketing expenditures stock, Drug age^2, Drug age

Figure 10.103 – Excluded variables for product LI3 in model 6

By removing the interaction variables, we solved the multicollinearity issues.

Such as with product LI3, SPSS excluded the same two variables in product LI4 (figure 10.104):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock	-23,270[b]	-,655	,519	-,132	8,087E-7
	Ln Average competitors price per DDD	1,770[b]	,480	,635	,098	7,578E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Laptop based materials (% of times used in calls), Increase / Will begin to prescribe (% of calls), Year 2013 (dummy), Quarter 2 (dummy), Printed material (% of times used in calls), Very useful (% of calls), Ln Avg number of products presented during the calls, Quarter 3 (dummy), Ipad / Tablet (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Global marketing expenditures stock x Ln Average drug price, Ln Global marketing expenditures flow, Ln Competitive global marketing expenditures stock, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Average drug price per DDD, Year 2014 (dummy), Drug age^2, Drug age

Figure 10.104 – Excluded variables for product LI4 in model 6

The multicollinearity issue was solved, once more time, by removing the two interaction variables from the list of independent variables.

Finally, in the case of product LI5, SPSS excluded the two interaction variables (figure 10.105).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Global marketing expenditures stock x Ln Average drug price	23,938[b]	1,865	,074	,356	3,018E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	16,536[b]	1,480	,152	,289	4,180E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Laptop based materials (% of times used in calls), Very useful (% of calls), Ln Sales in DDDs lagged two periods, Ln Avg number of products presented during the calls, Year 2014 (dummy), Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Printed material (% of times used in calls), Quarter 3 (dummy), Increase / Will begin to prescribe (% of calls), Ln Competitive global marketing expenditures stock, Ln Sales in DDDs lagged one period, Ln Global marketing expenditures flow, Year 2013 (dummy), Ln Global marketing expenditures stock, Ln Average drug price per DDD, Ln Average competitors price per DDD, Drug age^2, Drug age

Figure 10.105 – Excluded variables for product LI4 in model 6

Tables 10.63, 10.64, 10.65 and 10.66 summarize the coefficients obtained in Model 6.

Table 10.63 – Summary of Model 6 – Market 1 - Blood

Model specification			Model 6											
			Product BL1				Product BL2				Product BL3			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			5,697	---	No	No	9,642	---	Yes	Yes	1,605	---	---	---
Lagged sales	Ln Sales in DDDs lagged one period		0,244	Yes	No	No	-0,251	No	No	No	0,016	Yes	---	---
	Ln Sales in DDDs lagged two periods		0,057	Yes	No	No	0,085	Yes	No	No	0,123	Yes	---	---
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	0,009	Yes	No	No	0,001	Yes	No	No	0,141	Yes	---	---
	Competitive	Ln Competitive marketing expenditures flow	0,038	No	No	No	0,047	No	No	No	-0,243	Yes	---	---
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	-0,039	No	No	No	0,089	Yes	No	No	Removed due to multicollinearity			
	Competitive	Ln Competitive global marketing expenditures stock	0,208	No	No	No	0,025	No	No	No	Removed due to multicollinearity			
Price	Own	Ln Average drug price per DDD	0,180	No	No	No	-0,568	Yes	No	No	2,439	No	---	---
	Competitors	Ln Average competitors drug price per DDD	-2,234	No	Yes	Yes	0,058	Yes	No	No	Removed due to multicollinearity			
Drug age		Drug age	0,012	Yes	No	No	0,098	Yes	No	No	0,046	Yes	---	---
		Drug age squared	0,0001	No	No	No	-0,001	Yes	Yes	Yes	Removed due to multicollinearity			
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Policy change		Public reimbursement	0,452	Yes	Yes	Yes	-0,104	No	No	No	5,588	Yes	---	---
Additional variables	Ipad / Tablet (% of times used in calls)		0,016	---	No	No	0,649	---	No	No	-0,883	---	---	---
	Laptop based materials (% of times used in calls)		0,400	---	No	No	-0,537	---	No	No	-3,694	---	---	---
	Printed material (% of times used in calls)		0,220	---	No	No	0,336	---	Yes	Yes	-0,853	---	---	---
	Very useful (% of calls)		-0,146	---	No	No	0,031	---	No	No	0,526	---	---	---
	Increase / Will begin to prescribe (% of calls)		0,095	---	No	No	-0,0001	---	No	No	0,239	---	---	---
	Ln Avg number of products presented during the calls		-0,262	---	No	No	-0,049	---	No	No	0,404	---	---	---
Temporal dummies		Quarter 2	0,049	---	No	No	0,074	---	No	No	0,230	---	---	---
		Quarter 3	0,101	---	No	No	0,206	---	Yes	Yes	0,234	---	---	---
		Quarter 4	0,216	---	No	No	0,376	---	Yes	Yes	0,372	---	---	---
		Year 2013	0,223	---	No	No	0,457	---	Yes	Yes	N/A (product launched in 2014)			
		Year 2014	0,386	---	No	No	0,892	---	Yes	Yes				
		Year 2015	0,740	---	No	No	1,217	---	Yes	Yes	0,827	---	---	---
Adjusted R^2			0,997				0,986				0,999			
ANOVA Sig.			0,000				0,000				---			

Table 10.64 – Summary of Model 6 – Market 2 - Pancreas

Model specification			Model 6																	
			Product PA1				Product PA2				Product PA3				Product PA4				Product PA5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			22,921	---	Yes	Yes	26,755	---	Yes	Yes	21,201	---	Yes	Yes	17,666	---	No	No	16,048	---	Yes	Yes
Lagged sales	Ln Sales in DDDs lagged one period		-0,474	No	Yes	Yes	-0,459	No	Yes	Yes	-0,612	No	Yes	Yes	0,009	Yes	No	No	-0,432	No	Yes	Yes
	Ln Sales in DDDs lagged two periods		0,109	Yes	No	No	-0,055	No	No	No	-0,175	No	No	No	0,000	Yes	No	No	-0,105	No	No	No
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	0,021	Yes	No	No	0,036	Yes	No	No	-0,099	No	Yes	Yes	0,099	Yes	No	No	0,059	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	-0,027	Yes	No	No	0,016	No	No	No	0,120	Yes	Yes	Yes	0,115	No	No	No	0,018	No	No	No
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	0,194	Yes	No	No	-0,138	No	No	No	0,121	Yes	No	No	0,594	Yes	No	No	0,039	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	-0,028	Yes	No	No	0,132	No	No	No	-0,022	Yes	No	No	0,783	No	No	No	0,317	No	No	No
Price	Own	Ln Average drug price per DDD	9,171	No	No	No	-19,519	Yes	No	Yes	2,598	No	No	No	Constant (no variation)				-6,123	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	-23,990	No	No	No	4,207	Yes	No	No	-0,435	No	No	No	-161,32	No	No	No	0,692	Yes	No	No
Drug age		Drug age	-0,017	No	No	No	-0,026	No	No	No	0,026	Yes	No	No	0,170	Yes	No	No	-0,012	No	No	No
		Drug age squared	-0,0002	Yes	No	No	-0,00005	Yes	No	No	-0,0003	Yes	Yes	Yes	-0,002	Yes	No	No	0,0001	No	No	No
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Additional variables	Ipad / Tablet (% of times used in calls)		0,186	---	No	No	0,187	---	No	No	-0,305	---	No	No	0,099	---	No	No	-0,010	---	No	No
	Laptop based materials (% of times used in calls)		0,397	---	No	No	-0,151	---	No	No	-0,280	---	No	No	0,114	---	No	No	0,033	---	No	No
	Printed material (% of times used in calls)		0,149	---	Yes	Yes	0,136	---	No	No	0,059	---	No	No	0,350	---	No	No	0,038	---	No	No
	Very useful (% of calls)		-0,002	---	No	No	-0,095	---	No	No	0,154	---	No	No	1,179	---	No	Yes	0,069	---	No	No
	Increase / Will begin to prescribe (% of calls)		-0,056	---	No	No	-0,058	---	No	No	-0,044	---	No	No	0,387	---	No	No	-0,004	---	No	No
	Ln Avg number of products presented during the calls		-0,060	---	No	No	-0,133	---	No	No	-0,131	---	No	No	-0,756	---	No	No	-0,008	---	No	No
Temporal dummies		Quarter 2	0,171	---	Yes	Yes	0,102	---	Yes	Yes	0,078	---	No	Yes	0,247	---	No	No	0,027	---	No	No
		Quarter 3	0,300	---	Yes	Yes	0,235	---	Yes	Yes	0,122	---	No	Yes	0,832	---	Yes	Yes	0,093	---	No	No
		Quarter 4	0,435	---	Yes	Yes	0,344	---	Yes	Yes	0,191	---	No	Yes	0,936	---	Yes	Yes	0,119	---	No	No
		Year 2013	0,504	---	Yes	Yes	0,379	---	Yes	Yes	0,213	---	No	No	N/A (product launched in 2013)				0,093	---	No	No
		Year 2014	0,356	---	No	No	0,184	---	No	No	0,469	---	No	No	1,078	---	No	No	0,000	---	No	No
		Year 2015	0,823	---	No	No	0,483	---	No	No	0,666	---	No	No	2,117	---	No	No	0,099	---	No	No
Adjusted R^2			0,674				0,643				0,828				0,961				0,218			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,129			

Table 10.65 – Summary of Model 6 – Market 3 - Heart

Model specification			Model 6																	
			Product HE1				Product HE2				Product HE3				Product HE4				Product HE5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			28,336	---	Yes	Yes	21,002	---	Yes	Yes	10,563	---	No	No	21,106	---	Yes	Yes	3,976	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,733	No	Yes	Yes	-0,494	No	Yes	Yes	-0,565	No	No	No	-0,087	No	No	No	0,057	Yes	No	No
	Ln Sales in DDDs lagged two periods		-0,314	No	No	No	0,095	Yes	No	No	0,799	Yes	No	No	0,069	Yes	No	No	0,009	Yes	No	No
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	0,019	Yes	No	No	0,002	Yes	No	No	-0,061	No	No	No	0,006	Yes	No	No	0,026	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	-0,061	Yes	No	Yes	-0,045	Yes	No	No	-0,022	Yes	No	No	-0,044	Yes	No	No	-0,024	Yes	No	No
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	0,108	Yes	Yes	Yes	0,064	Yes	No	No	0,386	Yes	No	No	0,819	Yes	Yes	Yes	0,026	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	0,013	No	No	No	-0,028	Yes	No	No	0,230	No	No	No	-0,394	Yes	Yes	Yes	0,174	No	No	No
Price	Own	Ln Average drug price per DDD	1,065	No	No	No	0,442	No	No	No	-2,671	Yes	No	No	-4,130	Yes	No	Yes	-0,249	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	0,015	Yes	No	No	-0,075	No	No	No	-6,700	No	No	No	-1,132	No	No	Yes	-2,748	No	No	No
Drug age		Drug age	0,034	Yes	No	No	-0,009	No	No	No	-0,063	No	No	No	-0,042	No	Yes	Yes	0,107	Yes	Yes	Yes
		Drug age squared	-0,0002	Yes	No	Yes	-0,0002	Yes	No	No	Removed due to multicollinearity				Removed due to multicollinearity				-0,001	Yes	Yes	Yes
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				0,410	Yes	No	No	0,634	Yes	Yes	Yes	Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Policy change	Loss of exclusivity		Not applicable				Not applicable				-0,198	Yes	No	No	-0,161	Yes	Yes	Yes	Not applicable			
Additional variables	Ipad / Tablet (% of times used in calls)		0,096	---	No	No	0,170	---	No	No	0,086	---	No	No	Missing information				-0,250	---	No	No
	Laptop based materials (% of times used in calls)		0,177	---	No	No	-1,155	---	No	No	Missing information								-0,548	---	No	No
	Printed material (% of times used in calls)		0,013	---	No	No	0,114	---	No	No	0,009	---	No	No					0,166	---	No	No
	Very useful (% of calls)		-0,118	---	No	No	-0,029	---	No	No	0,034	---	No	No					0,416	---	No	Yes
	Increase / Will begin to prescribe (% of calls)		-0,002	---	No	No	0,064	---	No	No	0,040	---	No	No					-0,106	---	No	No
	Ln Avg number of products presented during the calls		0,104	---	No	No	0,038	---	No	No	-0,014	---	No	No					0,315	---	No	No
Temporal dummies		Quarter 2	0,104	---	Yes	Yes	0,144	---	Yes	Yes	0,192	---	No	No	0,063	---	No	No	0,042	---	0,491	No
		Quarter 3	0,161	---	Yes	Yes	0,203	---	Yes	Yes	0,094	---	No	No	0,102	---	No	No	0,044	---	0,609	No
		Quarter 4	0,240	---	Yes	Yes	0,349	---	Yes	Yes	0,380	---	No	No	0,190	---	No	No	0,161	---	0,195	No
		Year 2013	0,233	---	No	Yes	0,458	---	Yes	Yes	0,684	---	No	No	0,037	---	No	No	N/A (product launched in 2013)			
		Year 2014	0,533	---	Yes	Yes	0,888	---	Yes	Yes	1,376	---	No	No	0,228	---	No	No	0,100	---	No	No
		Year 2015	0,834	---	Yes	Yes	1,403	---	Yes	Yes	1,036	---	No	No	0,449	---	No	No	0,126	---	No	No
Adjusted R^2			0,872				0,623				0,815				0,984				0,991			
ANOVA Sig.			0,000				0,000				0,013				0,000				0,000			

Table 10.66 – Summary of Model 6 – Market 4 - Liver

Model specification			Model 6																	
			Product LI1				Product LI2				Product LI3				Product LI4				Product LI5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			27,974	---	Yes	Yes	16,858	---	Yes	Yes	19,204	---	Yes	Yes	7,336	---	No	No	3,473	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,482	No	Yes	Yes	-0,470	No	Yes	Yes	-0,359	No	Yes	Yes	-0,283	No	No	No	-0,063	No	No	No
	Ln Sales in DDDs lagged two periods		0,094	Yes	No	No	0,077	Yes	No	No	-0,141	No	No	No	0,092	Yes	No	No	0,309	Yes	No	Yes
Marketing expenditures flow	Own	Ln Global marketing expenditures flow	-0,009	No	No	No	-0,003	No	No	No	0,030	Yes	No	No	0,153	Yes	Yes	Yes	0,093	Yes	No	Yes
	Competitive	Ln Competitive marketing expenditures flow	0,049	No	No	No	-0,018	Yes	No	No	0,035	No	No	No	-0,098	Yes	No	No	0,088	No	No	Yes
Marketing expenditures stock	Own	Ln Global marketing expenditures stock	-0,121	No	No	No	0,013	Yes	No	No	0,141	Yes	No	No	0,126	Yes	No	No	0,184	Yes	No	No
	Competitive	Ln Competitive global marketing expenditures stock	-0,133	Yes	No	No	0,159	No	No	No	-0,040	Yes	No	No	0,109	No	No	No	0,187	No	No	No
Price	Own	Ln Average drug price per DDD	0,091	No	No	No	1,260	No	No	No	-1,385	Yes	No	No	-6,919	Yes	No	No	-3,412	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	0,784	Yes	No	No	0,449	Yes	No	No	-0,222	No	No	No	0,370	Yes	No	No	1,107	Yes	Yes	Yes
Drug age		Drug age	-0,045	No	No	No	-0,010	No	No	No	0,006	Yes	No	No	0,010	Yes	No	No	0,010	Yes	No	No
		Drug age squared	0,0001	No	No	No	-0,0001	Yes	No	No	-0,0001	Yes	No	No	-0,0003	Yes	No	Yes	-0,0003	Yes	No	Yes
Marketing expenditures interactions	Ln Global marketing expenditures stock x Ln Average drug price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Additional variables	Ipad / Tablet (% of times used in calls)		0,041	---	No	No	0,274	---	No	No	0,002	---	No	No	0,012	---	No	No	0,058	---	No	No
	Laptop based materials (% of times used in calls)		0,510	---	No	No	0,057	---	No	No	-0,031	---	No	No	-0,633	---	No	No	-0,368	---	No	No
	Printed material (% of times used in calls)		-0,055	---	No	No	0,073	---	No	No	-0,058	---	No	No	0,061	---	No	No	0,115	---	No	No
	Very useful (% of calls)		0,018	---	No	No	0,020	---	No	No	-0,128	---	No	No	-0,318	---	No	No	-0,273	---	No	No
	Increase / Will begin to prescribe (% of calls)		0,196	---	No	No	-0,060	---	No	No	0,242	---	Yes	Yes	0,086	---	No	No	0,091	---	No	No
	Ln Avg number of products presented during the calls		0,085	---	No	No	-0,053	---	No	No	0,112	---	No	No	0,233	---	No	No	-0,065	---	No	No
Temporal dummies		Quarter 2	0,122	---	No	No	0,152	---	Yes	Yes	0,057	---	No	No	0,096	---	Yes	Yes	0,188	---	Yes	Yes
		Quarter 3	0,250	---	No	No	0,254	---	Yes	Yes	0,169	---	No	Yes	0,167	---	Yes	Yes	0,258	---	Yes	Yes
		Quarter 4	0,316	---	No	No	0,410	---	Yes	Yes	0,194	---	No	No	0,257	---	Yes	Yes	0,385	---	Yes	Yes
		Year 2013	0,239	---	Yes	Yes	0,538	---	Yes	Yes	0,192	---	No	No	0,343	---	Yes	Yes	0,456	---	Yes	Yes
		Year 2014	0,714	---	No	Yes	1,041	---	Yes	Yes	0,557	---	No	Yes	0,603	---	Yes	Yes	0,938	---	Yes	Yes
		Year 2015	1,097	---	No	No	1,535	---	Yes	Yes	0,844	---	No	Yes	1,021	---	Yes	Yes	1,280	---	Yes	Yes
Adjusted R^2			0,194				0,534				0,421				0,953				0,743			
ANOVA Sig.			0,158				0,002				0,013				0,000				0,000			

10.5.3.2. Results

Based on the four tables shown above, we prepared a summary of results for a better interpretation, shown below in table 10.67.

Table 10.67 – Summary of Model 6 results

	Market 1 - Blood (3 products)				Market 2 - Pancreas (5 products)				Market 3 - Heart (5 products)				Market 4 - Liver (5 products)				Global (18 products)			
	% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities		% cases with...		Average elasticities	
	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.
Ln Sales in DDDs lagged one period	66,7%	0,0%	0,003	0,130	20,0%	0,0%	-0,394	0,009	20,0%	0,0%	-0,364	0,057	0,0%	0,0%	-0,332	N/A	22,2%	0,0%	-0,302	0,081
Ln Sales in DDDs lagged two periods	100,0%	0,0%	0,088	0,088	40,0%	0,0%	-0,045	0,109	80,0%	0,0%	0,131	0,243	80,0%	0,0%	0,086	0,086	72,2%	0,0%	0,063	0,137
Ln Global marketing expenditures flow	100,0%	0,0%	0,050	0,050	80,0%	0,0%	0,023	0,023	80,0%	0,0%	-0,002	-0,002	60,0%	20,0%	0,053	0,081	77,8%	5,6%	0,029	0,031
Ln Competitive marketing expenditures flow	33,3%	0,0%	-0,053	-0,243	40,0%	20,0%	0,048	-0,006	100,0%	0,0%	-0,039	-0,050	40,0%	0,0%	0,011	-0,098	55,6%	5,6%	-0,003	-0,072
Ln Global marketing expenditures stock	50,0%	0,0%	0,025	0,089	80,0%	0,0%	0,162	0,237	100,0%	40,0%	0,281	0,281	80,0%	0,0%	0,069	0,116	82,4%	11,8%	0,153	0,207
Ln Competitive global marketing expenditures stock	0,0%	0,0%	0,116	N/A	40,0%	0,0%	0,236	N/A	40,0%	20,0%	-0,001	-0,136	40,0%	0,0%	0,056	-0,133	35,3%	5,9%	0,099	-0,136
Ln Average drug price per DDD	33,3%	0,0%	0,684	-0,568	50,0%	0,0%	-3,468	-19,519	60,0%	0,0%	-1,109	-2,190	60,0%	0,0%	-2,073	-2,906	52,9%	0,0%	-1,631	-4,512
Ln Average competitors drug price per DDD	50,0%	0,0%	-1,088	0,058	40,0%	0,0%	-36,17	-4,882	20,0%	0,0%	-2,128	N/A	80,0%	20,0%	0,498	0,780	47,1%	5,9%	-11,25	-2,141
Drug age	100,0%	0,0%	0,052	0,052	40,0%	0,0%	0,028	0,060	40,0%	20,0%	0,005	0,071	60,0%	0,0%	-0,006	0,003	55,6%	5,6%	0,016	0,044
Drug age squared	50,0%	50,0%	0,000	-0,001	80,0%	20,0%	-0,001	-0,001	100,0%	33,3%	-0,001	-0,001	80,0%	0,0%	0,000	0,000	80,0%	20,0%	0,000	-0,001
Ln Global marketing expenditures flow x Ln Average drug price per DDD	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	100,0%	50,0%	0,522	0,522	N/A	N/A	N/A	N/A	100,0%	50,0%	0,522	0,522
Ln Global marketing expenditures flow x Ln Average competitors price per DDD	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Public reimbursement	66,7%	33,3%	1,979	3,020	---	---	---	---	---	---	---	---	---	---	---	---	66,7%	33,3%	1,979	3,020
Loss of exclusivity	---	---	---	---	---	---	---	---	100,0%	50,0%	-0,180	-0,180	---	---	---	---	100,0%	50,0%	-0,180	-0,180
Ipad / Tablet (% of times used in calls)	---	---	-0,072	---	---	---	0,031	---	---	---	0,026	---	---	---	0,077	---	---	---	0,025	---
Laptop based materials (% of times used in calls)	---	---	-1,277	---	---	---	0,023	---	---	---	-0,509	---	---	---	-0,093	---	---	---	-0,357	---
Printed material (% of times used in calls)	---	---	-0,099	---	---	---	0,147	---	---	---	0,076	---	---	---	0,027	---	---	---	0,051	---
Very useful (% of calls)	---	---	0,137	---	---	---	0,261	---	---	---	0,076	---	---	---	-0,136	---	---	---	0,079	---
Increase / Will begin to prescribe (% of calls)	---	---	0,111	---	---	---	0,045	---	---	---	-0,001	---	---	---	0,111	---	---	---	0,065	---
Ln Avg number of products presented during the calls	---	---	0,031	---	---	---	-0,217	---	---	---	0,111	---	---	---	0,062	---	---	---	-0,014	---

10.5.4. Model 7 (Model 4 with expenditures disaggregation + new variables)

10.5.4.1. Procedures and outputs

Starting with product BL1, SPSS excluded three variables (figure 10.106):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	1,652[b]	1,632	,119	,351	6,372E-5
	Ln Average competitors price per DDD	1,867[b]	2,065	,053	,428	7,440E-5
	Drug age	3,333[b]	2,180	,042	,447	2,549E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Very useful (% of calls), Year 2014 (dummy), Quarter 2 (dummy), Ln Journal advertising flow, Ln Competitive global marketing expenditures flow, Ln Mailing flow, Laptop based materials (% of times used in calls), Ln Other marketing expenditures stock, Quarter 3 (dummy), Year 2013 (dummy), Ln Drug price x drug age, Increase / Will begin to prescribe (% of calls), Ln Competitive global marketing expenditures stock, Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Ln Detailing flow (calls), Ln Global marketing expenditures stock x Ln Average competitors price, Public reimbursement (dummy), Ln Detailing stock (calls), Ln Sales in DDDs lagged two periods, Ln Drug price x Ln Detailing stock, Ln Sales in DDDs lagged one period, Drug age^2, Ln Drug price x Ln Detailing flow

Figure 10.106 – Excluded variables for product BL1 in model 7 – iteration 1

We started by removing the variables Drug age squared and Ln Global marketing expenditures stock x Ln Average competitors price per DDD, as sources of multicollinearity in many previous models. SPSS then excluded one variable (figure 10.107):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	1,649[b]	1,515	,146	,328	5,564E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Very useful (% of calls), Year 2014 (dummy), Quarter 2 (dummy), Ln Journal advertising flow, Ln Competitive global marketing expenditures flow, Ln Mailing flow, Laptop based materials (% of times used in calls), Ln Other marketing expenditures stock, Quarter 3 (dummy), Year 2013 (dummy), Ln Drug price x drug age, Increase / Will begin to prescribe (% of calls), Ln Competitive global marketing expenditures stock, Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Ln Detailing flow (calls), Ln Detailing stock (calls), Public reimbursement (dummy), Ln Average competitors price per DDD, Ln Sales in DDDs lagged two periods, Ln Drug price x Ln Detailing stock, Ln Sales in DDDs lagged one period, Drug age, Ln Drug price x Ln Detailing flow

Figure 10.107 – Excluded variables for product BL1 in model 7 – iteration 2

We suspected that the source of this exclusion was the interaction variable Ln Average drug price per DDD x Ln Detailing stock. After removing this variable, no additional excluded variables were detected.

In the case of product BL2, the excluded variables were the following (figure 10.108):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	-1,895[b]	-,828	,418	-,187	4,249E-5
	Ln Drug price x Ln Detailing stock	2,405[b]	,789	,440	,178	2,401E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	4,550[b]	1,470	,158	,320	2,159E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Mailing flow, Ln Journal advertising flow, Ln Avg number of products presented during the calls, Quarter 2 (dummy), Laptop based materials (% of times used in calls), Ln Detailing stock (calls), Ln Detailing flow (calls), Year 2013 (dummy), Ipad / Tablet (% of times used in calls), Very useful (% of calls), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Other marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Year 2014 (dummy), Public reimbursement (dummy), Ln Competitive global marketing expenditures stock, Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Average competitors price per DDD, Ln Sales in DDDs lagged one period, Ln Drug price x drug age, Drug age^2, Ln Drug price x Ln Detailing flow

Figure 10.108 – Excluded variables for product BL2 in model 7 – iteration 1

Given our experience with Model 4 and Model 5 (similar to Model 7), we removed the variables Drug age squared, Ln Drug price x Ln Detailing stock, and Ln Global marketing expenditures stock x Ln Average competitors price. SPSS then excluded another variable (figure 10.109):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	-4,512[b]	-2,799	,011	-,531	9,173E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Mailing flow, Ln Journal advertising flow, Ln Avg number of products presented during the calls, Quarter 2 (dummy), Laptop based materials (% of times used in calls), Ln Detailing stock (calls), Ln Detailing flow (calls), Year 2013 (dummy), Ipad / Tablet (% of times used in calls), Very useful (% of calls), Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Other marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Year 2014 (dummy), Public reimbursement (dummy), Ln Competitive global marketing expenditures stock, Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Average competitors price per DDD, Ln Sales in DDDs lagged one period, Ln Drug price x drug age, Ln Drug price x Ln Detailing flow

Figure 10.109 – Excluded variables for product BL2 in model 7 – iteration 2

By removing the interaction variable Ln Average drug price per DDD x Drug age, no more issues of multicollinearity were detected.

In the case of product BL3, SPSS excluded a substantial number of variables, a similar situation as in Models 4 and 5 (figure 10.110).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Sales in DDDs lagged two periods	.[b]	.	.	.	,000
	Ln Detailing flow (calls)	.[b]	.	.	.	,000
	Ln Detailing stock (calls)	.[b]	.	.	.	,000
	Ln Other marketing expenditures stock	.[b]	.	.	.	,000
	Ln Competitive global marketing expenditures stock	.[b]	.	.	.	,000
	Ln Average drug price per DDD	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000
	Drug age^2	.[b]	.	.	.	,000
	Ln Drug price x drug age	.[b]	.	.	.	,000
	Quarter 3 (dummy)	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ipad / Tablet (% of times used in calls), Quarter 4 (dummy), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 2 (dummy), Ln Drug price x Ln Detailing flow, Laptop based materials (% of times used in calls), Increase / Will begin to prescribe (% of calls), Ln Avg number of products presented during the calls, Ln Journal advertising flow, Printed material (% of times used in calls), Ln Drug price x Ln Detailing stock, Public reimbursement (dummy), Very useful (% of calls), Ln Mailing flow, Ln Competitive global marketing expenditures flow, Ln Sales in DDDs lagged one period

Figure 10.110 – Excluded variables for product BL3 in model 7 – iteration 1

We started by removing the variables that previously had demonstrated to be a source of multicollinearity in the previous products and similar models: Drug age squared, Ln Average drug price per DDD x Ln Detailing stock, Ln Average drug price per DDD x Drug age, and Ln Global marketing expenditures stock x Ln Average competitors price per DDD. SPSS kept excluding some variables (figure 10.111):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Sales in DDDs lagged two periods	.[b]	.	.	.	,000
	Ln Detailing stock (calls)	.[b]	.	.	.	,000
	Ln Other marketing expenditures stock	.[b]	.	.	.	,000
	Ln Average drug price per DDD	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000
	Quarter 3 (dummy)	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ipad / Tablet (% of times used in calls), Quarter 4 (dummy), Quarter 2 (dummy), Ln Drug price x Ln Detailing flow, Laptop based materials (% of times used in calls), Ln Competitive global marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Ln Avg number of products presented during the calls, Ln Journal advertising flow, Ln Mailing flow, Printed material (% of times used in calls), Ln Competitive global marketing expenditures flow, Public reimbursement (dummy), Very useful (% of calls), Ln Sales in DDDs lagged one period, Ln Detailing flow (calls)

Figure 10.111 – Excluded variables for product BL3 in model 7 – iteration 2

We then removed the variables Ln Average drug price per DDD x Ln Detailing flow, and Ln Sales in DDDs lagged two periods. SPSS kept excluding the following variables (figure 10.112):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing stock (calls)	.[b]	.	.	.	,000
	Ln Competitive global marketing expenditures stock	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000
	Quarter 3 (dummy)	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ipad / Tablet (% of times used in calls), Quarter 4 (dummy), Quarter 2 (dummy), Laptop based materials (% of times used in calls), Ln Other marketing expenditures stock, Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Ln Journal advertising flow, Public reimbursement (dummy), Ln Mailing flow, Printed material (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Detailing flow (calls), Very useful (% of calls), Ln Sales in DDDs lagged one period, Ln Average drug price per DDD

Figure 10.112 – Excluded variables for product BL3 in model 7 – iteration 3

We then removed the variables Quarter 3 (dummy) and Ln Competitive global marketing expenditures stock, which reduced the excluded variables to three (figure 10.113):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing stock (calls)	.[b]	.	.	.	,000
	Ln Average competitors price per DDD	.[b]	.	.	.	,000
	Drug age	.[b]	.	.	.	,000

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ipad / Tablet (% of times used in calls), Quarter 4 (dummy), Quarter 2 (dummy), Laptop based materials (% of times used in calls), Ln Other marketing expenditures stock, Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Ln Journal advertising flow, Public reimbursement (dummy), Ln Mailing flow, Printed material (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Detailing flow (calls), Very useful (% of calls), Ln Sales in DDDs lagged one period, Ln Average drug price per DDD

Figure 10.113 – Excluded variables for product BL3 in model 7 – iteration 4

Finally, we removed the variables Quarter 2 (dummy) and Quarter 4 (dummy) (which were allowing an almost perfect linear combination to calculate drug age), and Ln Average competitors price per DDD, and no more issues of multicollinearity were found.

Moving to product PA1, SPSS excluded two variables (figure 10.114):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing stock	4,977[b]	,194	,848	,044	8,700E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	-6,075[b]	-,638	,531	-,145	6,177E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Laptop based materials (% of times used in calls), Ln Avg number of products presented during the calls, Very useful (% of calls), Year 2013 (dummy), Quarter 3 (dummy), Ln Mailing flow, Ln Detailing flow (calls), Ipad / Tablet (% of times used in calls), Increase / Will begin to prescribe (% of calls), Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Journal advertising flow, Ln Sales in DDDs lagged two periods, Ln Other marketing expenditures stock, Ln Detailing stock (calls), Ln Competitive global marketing expenditures flow, Ln Average drug price per DDD, Ln Competitive global marketing expenditures stock, Ln Drug price x drug age, Year 2014 (dummy), Drug age^2, Ln Drug price x Ln Detailing flow, Ln Average competitors price per DDD, Drug age

Figure 10.114 – Excluded variables for product PA1 in model 7

By removing these two variables from the list of independent variables, no additional multicollinearity was detected.

In the case of product PA2, SPSS excluded three variables (figure 10.115):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	-32,665[b]	-1,159	,260	-,251	8,053E-6
	Ln Drug price x Ln Detailing stock	-41,625[b]	-1,336	,197	-,286	6,460E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	-63,866[b]	-2,576	,018	-,499	8,342E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Increase / Will begin to prescribe (% of calls), Ln Mailing flow, Laptop based materials (% of times used in calls), Printed material (% of times used in calls), Ln Journal advertising flow, Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Year 2013 (dummy), Very useful (% of calls), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Quarter 3 (dummy), Ln Avg number of products presented during the calls, Ipad / Tablet (% of times used in calls), Ln Competitive global marketing expenditures stock, Ln Detailing flow (calls), Ln Average competitors price per DDD, Ln Detailing stock (calls), Ln Other marketing expenditures stock, Year 2014 (dummy), Ln Drug price x drug age, Drug age^2, Ln Average drug price per DDD, Ln Drug price x Ln Detailing flow

Figure 10.115 – Excluded variables for product PA2 in model 7

By removing the two interaction variables in additional to the interaction variable Average Drug price x Drug age, no more multicollinearity issues were detected.

Moving to product PA3, SPSS excluded three variables (figure 10.116):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	3,475[b]	,279	,783	,062	2,333E-5
	Drug age	-11,459[b]	-,506	,619	-,112	6,982E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	-10,251[b]	-,855	,403	-,188	2,437E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Detailing stock (calls), Increase / Will begin to prescribe (% of calls), Printed material (% of times used in calls), Ln Journal advertising flow, Ln Mailing flow, Very useful (% of calls), Laptop based materials (% of times used in calls), Ln Detailing flow (calls), Ln Other marketing expenditures stock, Quarter 3 (dummy), Ln Avg number of products presented during the calls, Ipad / Tablet (% of times used in calls), Year 2013 (dummy), Quarter 2 (dummy), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures flow, Ln Average competitors price per DDD, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Ln Drug price x drug age, Ln Drug price x Ln Detailing flow, Ln Drug price x Ln Detailing stock

Figure 10.116 – Excluded variables for product PA3 in model 7

Given our experience with this model, we removed the interaction variables Ln Global marketing expenditures stock x Ln Average competitors' price, Ln Average drug price per DDD x Drug age, and Ln Average drug price per DDD x Ln Detailing stock, which resulted in no additional variables excluded.

In relation to product PA4, SPSS excluded three variables (figure 10.117):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing stock (calls)	-20164,825[b]	-1,715	,130	-,544	7,897E-12
	Drug age	.[b]	.	.	.	,000
	Ln Drug price x Ln Detailing flow	538,433[b]	,027	,979	,010	3,909E-12

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Laptop based materials (% of times used in calls), Quarter 3 (dummy), Ln Other marketing expenditures stock, Ln Journal advertising flow, Very useful (% of calls), Printed material (% of times used in calls), Ln Sales in DDDs lagged one period, Ln Mailing flow, Quarter 4 (dummy), Ln Competitive global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Quarter 2 (dummy), Ln Sales in DDDs lagged two periods, Ln Detailing flow (calls), Year 2014 (dummy), Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Ln Drug price x Ln Detailing stock, Drug age^2, Ln Drug price x drug age, Ln Global marketing expenditures stock x Ln Average competitors price

Figure 10.117 – Excluded variables for product PA4 in model 7 – iteration 1

Leeflang & Wieringa (2010) noted that interactions between variables may be a source of multicollinearity, and therefore some should be removed. Following this principle, and using our experience with the data and intuition, we decided to remove the following variables, in order to solve the multicollinearity issues: Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, Ln Average drug price per DDD x Ln Detailing stock, and Ln Average drug price per DDD x Drug age. One additional interaction variable was excluded by SPSS. After its removal, no more issues were detected (figure 10.118).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing flow	579,060[b]	,031	,976	,011	3,910E-12

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Laptop based materials (% of times used in calls), Quarter 3 (dummy), Ln Other marketing expenditures stock, Ln Journal advertising flow, Very useful (% of calls), Printed material (% of times used in calls), Ln Sales in DDDs lagged one period, Ln Mailing flow, Quarter 4 (dummy), Ln Competitive global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Quarter 2 (dummy), Ln Sales in DDDs lagged two periods, Ln Detailing flow (calls), Year 2014 (dummy), Ln Competitive global marketing expenditures stock, Ln Average competitors price per DDD, Ln Detailing stock (calls), Drug age^2, Drug age

Figure 10.118 – Excluded variables for product PA4 in model 7 – iteration 2

Moving to product PA5, SPSS removed three variables (figure 10.119):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-14,012[b]	-,935	,361	-,205	8,198E-5
	Ln Average competitors price per DDD	-10,763[b]	-,479	,637	-,106	3,758E-5
	Drug age	4,794[b]	,114	,911	,025	1,081E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ipad / Tablet (% of times used in calls), Ln Mailing flow, Ln Sales in DDDs lagged two periods, Printed material (% of times used in calls), Ln Other marketing expenditures stock, Very useful (% of calls), Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Quarter 2 (dummy), Year 2013 (dummy), Ln Sales in DDDs lagged one period, Laptop based materials (% of times used in calls), Ln Journal advertising flow, Ln Detailing flow (calls), Ln Global marketing expenditures stock x Ln Average competitors price, Quarter 3 (dummy), Ln Competitive global marketing expenditures flow, Ln Detailing stock (calls), Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Ln Drug price x drug age, Drug age^2, Ln Drug price x Ln Detailing flow, Ln Drug price x Ln Detailing stock

Figure 10.119 – Excluded variables for product PA5 in model 7

We started by removing the variables that previously provoked more sources of multicollinearity: Ln Average drug price per DDD x Ln Detailing stock, Ln Average drug price per DDD x Drug age, and Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, decision that proved to be adequate (no additional variables excluded).

In the case of product HE1, SPSS excluded three variables (figure 10.120):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow (calls)	-8,814[b]	-1,355	,190	-,290	6,190E-5
	Ln Detailing stock (calls)	6,136[b]	,358	,724	,080	9,693E-6
	Ln Drug price x drug age	-38,232[b]	-,975	,341	-,213	1,773E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Increase / Will begin to prescribe (% of calls), Ln Other marketing expenditures stock, Laptop based materials (% of times used in calls), Ln Mailing flow, Ln Journal advertising flow, Quarter 3 (dummy), Very useful (% of calls), Printed material (% of times used in calls), Year 2013 (dummy), Quarter 2 (dummy), Ln Drug price x Ln Detailing flow, Ln Competitive global marketing expenditures stock, Ln Avg number of products presented during the calls, Ln Competitive global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Ln Global marketing expenditures stock x Ln Average competitors price, Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Drug price x Ln Detailing stock, Year 2014 (dummy), Ln Average drug price per DDD, Drug age^2, Drug age, Ln Average competitors price per DDD

Figure 10.120 – Excluded variables for product HE1 in model 7 – iteration 1

By removing the interaction variables Ln Average drug price per DDD x Ln Detailing stock, Ln Average drug price per DDD x Drug age, and Ln Global marketing expenditures stock x Ln Average competitors price per DDD, we almoved solved the multicollinearity issues. Then SPSS excluded the remaining interaction variable Ln Average drug price per DDD x Ln Detailing flow which, after removal from the list of independent variables, solved the multicollinearity problems (figure 10.121).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow (calls)	-8,878[b]	-1,379	,182	-,288	6,219E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Increase / Will begin to prescribe (% of calls), Ln Other marketing expenditures stock, Laptop based materials (% of times used in calls), Ln Mailing flow, Ln Journal advertising flow, Quarter 3 (dummy), Very useful (% of calls), Printed material (% of times used in calls), Year 2013 (dummy), Quarter 2 (dummy), Ln Drug price x Ln Detailing flow, Ln Competitive global marketing expenditures stock, Ln Avg number of products presented during the calls, Ln Competitive global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged one period, Ln Sales in DDDs lagged two periods, Ln Average competitors price per DDD, Ln Detailing stock (calls), Year 2014 (dummy), Ln Average drug price per DDD, Drug age^2, Drug age

Figure 10.121 – Excluded variables for product HE1 in model 7 – iteration 2

SPSS removed two variables in the case of product HE2 (figure 10.122):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average drug price per DDD	-10,849[b]	-,823	,421	-,186	2,663E-5
	Ln Drug price x drug age	-,648[b]	-,051	,960	-,012	2,926E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Other marketing expenditures stock, Ln Avg number of products presented during the calls, Ln Competitive global marketing expenditures flow, Quarter 2 (dummy), Very useful (% of calls), Ln Journal advertising flow, Ln Mailing flow, Ln Sales in DDDs lagged one period, Increase / Will begin to prescribe (% of calls), Laptop based materials (% of times used in calls), Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged two periods, Quarter 3 (dummy), Ln Competitive global marketing expenditures stock, Year 2013 (dummy), Ln Average competitors price per DDD, Ln Detailing flow (calls), Year 2014 (dummy), Ln Detailing stock (calls), Ln Drug price x Ln Detailing flow, Drug age^2, Ln Drug price x Ln Detailing stock, Drug age, Ln Global marketing expenditures stock x Ln Average competitors price

Figure 10.122 – Excluded variables for product HE2 in model 7

We removed the interaction variables Ln Average drug price per DDD x Drug age, Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, and Ln Average drug price per DDD x Ln Detailing stock, which solved the multicollinearity issues.

In the case of product HE3, SPSS removed three variables (figure 10.123):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing stock (calls)	6,479[b]	,899	,464	,536	9,159E-5
	Drug age^2	-50,905[b]	-1,097	,387	-,613	1,936E-6
	Ln Drug price x drug age	-34,455[b]	-,598	,611	-,389	1,706E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Detailing flow (calls), Ln Other marketing expenditures stock, Quarter 2 (dummy), Year 2014 (dummy), Increase / Will begin to prescribe (% of calls), Quarter 4 (dummy), Printed material (% of times used in calls), Ipad / Tablet (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Avg number of products presented during the calls, Ln Mailing flow, Very useful (% of calls), Year 2013 (dummy), Quarter 3 (dummy), Ln Competitive global marketing expenditures stock, Loss of exclusivity (dummy), Ln Average competitors price per DDD, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Average drug price per DDD, Drug age, Ln Drug price x Ln Detailing stock, Ln Drug price x Ln Detailing flow

Figure 10.123 – Excluded variables for product HE3 in model 7 – iteration 1

We removed the interaction variables Ln Average drug price per DDD x Ln Detailing stock, Ln Average drug price per DDD x Drug age, and Ln Global marketing expenditures stock x

Ln Average competitors' price per DDD. We ran the regression again and SPSS still removed the variables Drug age squared (figure 10.124).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age^2	-70,623[b]	-1,500	,231	-,655	1,511E-6

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Ln Detailing flow (calls), Ln Other marketing expenditures stock, Quarter 2 (dummy), Year 2014 (dummy), Increase / Will begin to prescribe (% of calls), Quarter 4 (dummy), Printed material (% of times used in calls), Ipad / Tablet (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Avg number of products presented during the calls, Ln Mailing flow, Very useful (% of calls), Year 2013 (dummy), Quarter 3 (dummy), Ln Competitive global marketing expenditures stock, Loss of exclusivity (dummy), Ln Average competitors price per DDD, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Detailing stock (calls), Ln Average drug price per DDD, Drug age, Ln Drug price x Ln Detailing flow

Figure 10.124 – Excluded variables for product HE3 in model 7 – iteration 2

After removing this variable, no more issues were detected.

In the case of product HE4, we noted that the dataset has very limited information available regarding the new variables. Therefore, we removed those variables, and as a consequence product HE4 in Model 7 will have the same outputs as in Model 5.

Moving to product HE5, SPSS removed two variables (figure 10.125):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Drug price x Ln Detailing stock	-18,879[b]	-2,606	,035	-,702	4,024E-6
	Ln Global marketing expenditures stock x Ln Average competitors price	7,219[b]	1,621	,149	,522	1,526E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Increase / Will begin to prescribe (% of calls), Ln Journal advertising flow, Ln Average drug price per DDD, Laptop based materials (% of times used in calls), Quarter 2 (dummy), Ln Detailing flow (calls), Ln Mailing flow, Ln Detailing stock (calls), Ln Avg number of products presented during the calls, Ipad / Tablet (% of times used in calls), Ln Average competitors price per DDD, Year 2014 (dummy), Quarter 3 (dummy), Very useful (% of calls), Printed material (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Other marketing expenditures stock, Ln Sales in DDDs lagged two periods, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Sales in DDDs lagged one period, Ln Drug price x drug age, Drug age, Ln Drug price x Ln Detailing flow

Figure 10.125 – Excluded variables for product HE5 in model 7

By removing these two interaction variables, we solved the multicollinearity issues.

Moving to product LI1, SPSS excluded four variables (figure 10.126).

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow (calls)	-23,843[b]	-1,165	,257	-,246	4,259E-5
	Ln Detailing stock (calls)	-25,175[b]	-,824	,419	-,177	1,973E-5
	Ln Average competitors price per DDD	-9,677[b]	-,316	,755	-,069	2,015E-5
	Ln Drug price x drug age	41,047[b]	1,406	,174	,293	2,040E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Journal advertising flow, Very useful (% of calls), Ipad / Tablet (% of times used in calls), Ln Sales in DDDs lagged two periods, Ln Mailing flow, Ln Sales in DDDs lagged one period, Quarter 3 (dummy), Year 2014 (dummy), Printed material (% of times used in calls), Quarter 2 (dummy), Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Ln Drug price x Ln Detailing flow, Laptop based materials (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Drug price x Ln Detailing stock, Year 2013 (dummy), Ln Other marketing expenditures stock, Ln Competitive global marketing expenditures stock, Ln Average drug price per DDD, Ln Global marketing expenditures stock x Ln Average competitors price, Drug age^2, Drug age

Figure 10.126 – Excluded variables for product LI1 in model 7

Given our experience with this model, we decided to remove the interaction variables Ln Average drug price per DDD x Ln Detailing stock, Ln Average drug price per DDD x Drug age, Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, and Ln Average drug price per DDD x Ln Detailing flow, which solved the multicollinearity issues. In the case of product LI2, SPSS excluded four variables (figure 10.127):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	13,881[b]	,847	,406	,182	4,200E-5
	Drug age	,101[b]	,003	,998	,001	7,425E-6
	Ln Drug price x Ln Detailing flow	-4,904[b]	-,443	,663	-,096	9,412E-5
	Ln Drug price x Ln Detailing stock	-17,640[b]	-,781	,444	-,168	2,219E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Ln Journal advertising flow, Ln Mailing flow, Laptop based materials (% of times used in calls), Printed material (% of times used in calls), Ln Avg number of products presented during the calls, Ipad / Tablet (% of times used in calls), Quarter 3 (dummy), Ln Other marketing expenditures stock, Year 2013 (dummy), Ln Sales in DDDs lagged two periods, Very useful (% of calls), Ln Sales in DDDs lagged one period, Quarter 2 (dummy), Ln Detailing flow (calls), Ln Competitive global marketing expenditures flow, Ln Detailing stock (calls), Ln Competitive global marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Ln Global marketing expenditures stock x Ln Average competitors price, Ln Average drug price per DDD, Year 2014 (dummy), Ln Drug price x drug age, Drug age^2

Figure 10.127 – Excluded variables for product LI2 in model 7

By removing the four interaction variables, we solved the multicollinearity problems.

Moving to product LI3, SPSS excluded two variables (figure 10.128):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Average competitors price per DDD	-,651[b]	-,045	,965	-,010	3,536E-5
	Ln Drug price x drug age	-11,486[b]	-,667	,513	-,151	2,460E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Printed material (% of times used in calls), Ln Detailing stock (calls), Laptop based materials (% of times used in calls), Ln Drug price x Ln Detailing flow, Ln Journal advertising flow, Ln Other marketing expenditures stock, Very useful (% of calls), Quarter 3 (dummy), Ln Sales in DDDs lagged two periods, Ln Mailing flow, Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Increase / Will begin to prescribe (% of calls), Ln Sales in DDDs lagged one period, Year 2013 (dummy), Quarter 2 (dummy), Ln Drug price x Ln Detailing stock, Year 2014 (dummy), Ln Competitive global marketing expenditures flow, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Competitive global marketing expenditures stock, Drug age^2, Ln Detailing flow (calls), Drug age, Ln Average drug price per DDD

Figure 10.128 – Excluded variables for product LI3 in model 7

To solve this multicollinearity problem, we removed two interaction variables: Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, and Ln Average drug price per DDD x Drug age, which resulted in no additional variables excluded.

In the case of product LI4, SPSS excluded three variables (figure 10.129):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Ln Detailing flow (calls)	-45,782[b]	-1,024	,318	-,223	6,255E-7
	Ln Detailing stock (calls)	39,934[b]	,356	,726	,079	1,036E-7
	Ln Drug price x drug age	-4,843[b]	-,030	,977	-,007	4,944E-8

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Laptop based materials (% of times used in calls), Increase / Will begin to prescribe (% of calls), Ln Journal advertising flow, Printed material (% of times used in calls), Ln Mailing flow, Year 2013 (dummy), Very useful (% of calls), Quarter 3 (dummy), Ln Other marketing expenditures stock, Quarter 2 (dummy), Ln Avg number of products presented during the calls, Ipad / Tablet (% of times used in calls), Ln Drug price x Ln Detailing flow, Ln Global marketing expenditures stock x Ln Average competitors price, Ln Competitive global marketing expenditures flow, Ln Average drug price per DDD, Ln Sales in DDDs lagged two periods, Ln Drug price x Ln Detailing stock, Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures stock, Year 2014 (dummy), Drug age^2, Ln Average competitors price per DDD, Drug age

Figure 10.129 – Excluded variables for product LI4 in model 7

By removing these three interaction variables from the regression model, no additional issues of multicollinearity were detected.

Finally, regarding product LI5, SPSS excluded three variables (figure 10.130):

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	Drug age	22,740[b]	1,405	,175	,300	1,725E-5
	Ln Drug price x Ln Detailing stock	14,596[b]	1,134	,270	,246	2,815E-5
	Ln Global marketing expenditures stock x Ln Average competitors price	6,662[b]	,523	,607	,116	3,014E-5

a. Dependent Variable: Ln Sales in DDDs

b. Predictors in the Model: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Laptop based materials (% of times used in calls), Very useful (% of calls), Ln Sales in DDDs lagged two periods, Ln Avg number of products presented during the calls, Year 2014 (dummy), Quarter 2 (dummy), Ln Competitive global marketing expenditures flow, Ipad / Tablet (% of times used in calls), Printed material (% of times used in calls), Quarter 3 (dummy), Ln Mailing flow, Ln Journal advertising flow, Increase / Will begin to prescribe (% of calls), Ln Other marketing expenditures stock, Ln Competitive global marketing expenditures stock, Ln Sales in DDDs lagged one period, Ln Detailing flow (calls), Year 2013 (dummy), Ln Detailing stock (calls), Ln Average drug price per DDD, Ln Average competitors price per DDD, Drug age^2, Ln Drug price x drug age, Ln Drug price x Ln Detailing flow

Figure 10.130 – Excluded variables for product LI5 in model 7

We decided to remove three interaction variables: Ln Average drug price per DDD x Ln Detailing stock, Ln Average drug price per DDD x Drug age, and Ln Global marketing expenditures stock x Ln Average competitors' price per DDD, which solved the multicollinearity issues. Tables 10.68, 10.69, 10.70 and 10.71 summarize the coefficients obtained in Model 7.

Table 10.68 – Summary of Model 7 – Market 1 - Blood

Model specification			Model 7											
			Product BL1				Product BL2				Product BL3			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			4,139	---	No	No	5,967	---	No	No	-1,683	---	---	---
Lagged sales	Ln Sales in DDDs lagged one period		0,297	Yes	No	No	-0,139	No	No	No	0,028	Yes	---	---
	Ln Sales in DDDs lagged two periods		-0,005	No	No	No	0,440	Yes	Yes	Yes	Removed due to multicollinearity			
Marketing expenditures flow	Own	Ln Detailing flow	0,012	Yes	No	No	0,214	Yes	No	No	0,127	Yes	---	---
		Ln Journal advertising flow	0,007	Yes	No	No	0,005	Yes	No	No	0,008	Yes	---	---
		Ln Direct marketing flow	0,008	Yes	No	No	-0,002	No	No	No	-0,009	No	---	---
	Competitive	Ln Competitive marketing expenditures flow	0,012	No	No	No	0,088	No	No	No	-0,158	Yes	---	---
Marketing expenditures stock	Own	Ln Detailing stock	0,334	Yes	No	No	0,139	Yes	No	No	0,353	Yes	---	---
		Ln Other marketing expenditures stock	-0,044	No	No	No	-0,106	No	No	Yes	0,249	Yes	---	---
	Competitive	Ln Competitive global marketing expenditures stock	-0,022	Yes	No	No	0,078	No	No	No	Removed due to multicollinearity			
Price	Own	Ln Average drug price per DDD	0,986	No	No	No	1,675	No	No	No	-0,743	Yes	---	---
	Competitors	Ln Average competitors drug price per DDD	-1,537	No	No	No	-0,140	No	No	No	Removed due to multicollinearity			
Drug age		Drug age	0,044	Yes	No	No	-0,020	No	No	No	0,129	Yes	---	---
		Drug age squared	Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		-0,008	No	No	No	-0,244	No	No	No	Removed due to multicollinearity			
	Ln Average drug price per DDD x Ln Detailing stock		Excluded due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Average drug price per DDD x Drug age		-0,014	Yes	No	No	Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Policy change		Public reimbursement	0,463	Yes	Yes	Yes	-0,208	No	No	Yes	4,354	Yes	---	---
Additional variables	Ipad / Tablet (% of times used in calls)		-0,031	---	No	No	0,345	---	No	No	0,153	---	---	---
	Laptop based materials (% of times used in calls)		0,727	---	No	No	-1,548	---	Yes	Yes	-1,403	---	---	---
	Printed material (% of times used in calls)		0,289	---	No	No	0,205	---	No	No	-0,345	---	---	---
	Very useful (% of calls)		-0,091	---	No	No	-0,147	---	No	No	-0,308	---	---	---
	Increase / Will begin to prescribe (% of calls)		-0,031	---	No	No	0,0357	---	No	No	0,117	---	---	---
	Ln Avg number of products presented during the calls		-0,362	---	No	No	-0,146	---	No	No	0,698	---	---	---
Temporal dummies		Quarter 2	0,024	---	No	No	0,062	---	No	No	Removed due to multicollinearity			
		Quarter 3	0,040	---	No	No	0,163	---	No	No				
		Quarter 4	0,137	---	No	No	0,389	---	Yes	Yes				
		Year 2013	0,199	---	No	No	0,545	---	Yes	Yes	N/A (product launched in 2014)			
		Year 2014	0,192	---	No	No	1,105	---	Yes	Yes				
		Year 2015	0,386	---	No	No	1,373	---	Yes	Yes	0,043	---	---	---
Adjusted R^2			0,997				0,986				1,000			
ANOVA Sig.			0,000				0,000				---			

Table 10.69 – Summary of Model 7 – Market 2 - Pancreas

Model specification			Model 7																	
			Product PA1				Product PA2				Product PA3				Product PA4				Product PA5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			31,267	---	Yes	Yes	24,512	---	Yes	Yes	25,818	---	Yes	Yes	11,758	---	No	No	14,986	---	No	Yes
Lagged sales	Ln Sales in DDDs lagged one period		-0,603	No	Yes	Yes	-0,486	No	Yes	Yes	-0,757	No	Yes	Yes	-0,072	No	No	No	-0,474	No	Yes	Yes
	Ln Sales in DDDs lagged two periods		0,027	No	No	No	0,184	Yes	No	No	-0,275	No	No	No	-0,070	No	No	No	-0,080	No	No	
Marketing expenditures flow	Own	Ln Detailing flow	0,061	Yes	No	No	-0,125	No	No	No	-0,049	No	No	No	0,597	Yes	No	No	0,344	Yes	No	No
		Ln Journal advertising flow	-0,006	No	No	No	0,006	Yes	Yes	Yes	0,004	Yes	No	No	-0,006	No	No	No	0,003	Yes	No	No
		Ln Direct marketing flow	-0,005	No	No	No	0,001	Yes	No	No	0,0004	Yes	No	No	0,015	Yes	No	No	-0,002	No	No	No
	Competitive	Ln Competitive marketing expenditures flow	0,004	No	No	No	0,020	No	No	No	0,075	No	No	No	-0,124	Yes	No	No	0,022	No	No	No
Marketing expenditures stock	Own	Ln Detailing stock	0,037	Yes	No	No	-0,203	No	No	No	0,049	Yes	No	No	1,728	Yes	No	No	0,099	Yes	No	No
		Ln Other marketing expenditures stock	0,013	Yes	No	No	0,043	Yes	No	No	0,030	Yes	No	No	-0,039	No	No	No	-0,027	No	No	No
	Competitive	Ln Competitive global marketing expenditures stock	-0,088	Yes	No	No	0,164	No	No	No	-0,107	Yes	No	No	0,946	No	No	No	0,275	No	No	No
Price	Own	Ln Average drug price per DDD	-0,089	Yes	No	No	-24,286	Yes	No	No	6,096	No	No	No	Constant (no variation)				-1,487	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	-22,866	No	No	No	3,912	Yes	No	No	-0,279	No	No	No	-163,61	No	No	No	2,608	Yes	No	No
Drug age		Drug age	-0,088	No	Yes	Yes	-0,023	No	No	No	0,031	Yes	No	No	0,142	Yes	No	No	-0,002	No	No	No
		Drug age squared	0,0000	Yes	No	No	-0,0001	Yes	No	No	-0,0004	Yes	Yes	Yes	-0,0004	Yes	No	No	-0,0001	Yes	No	No
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		-0,332	No	No	No	0,495	Yes	No	No	-0,301	No	No	No	Removed due to multicollinearity				-0,986	No	No	No
	Ln Average drug price per DDD x Ln Detailing stock		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Average drug price per DDD x Drug age		0,228	No	Yes	Yes	Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
Additional variables	Ipad / Tablet (% of times used in calls)		0,285	---	No	No	0,043	---	No	No	-0,394	---	No	No	0,295	---	No	No	0,004	---	No	No
	Laptop based materials (% of times used in calls)		0,040	---	No	No	-0,002	---	No	No	-0,130	---	No	No	0,998	---	No	No	0,182	---	No	No
	Printed material (% of times used in calls)		0,002	---	No	No	0,064	---	No	No	0,044	---	No	No	-0,021	---	No	No	-0,011	---	No	No
	Very useful (% of calls)		-0,196	---	No	No	-0,140	---	No	No	0,147	---	No	No	0,338	---	No	No	0,027	---	No	No
	Increase / Will begin to prescribe (% of calls)		0,156	---	No	No	0,050	---	No	No	-0,055	---	No	No	-0,636	---	No	No	-0,012	---	No	No
	Ln Avg number of products presented during the calls		0,076	---	No	No	-0,101	---	No	No	-0,120	---	No	No	-1,084	---	No	No	-0,050	---	No	No
Temporal dummies		Quarter 2	0,143	---	Yes	Yes	0,120	---	Yes	Yes	0,100	---	No	Yes	0,042	---	No	No	0,070	---	No	No
		Quarter 3	0,241	---	Yes	Yes	0,296	---	Yes	Yes	0,158	---	Yes	Yes	0,587	---	No	No	0,163	---	No	No
		Quarter 4	0,351	---	Yes	Yes	0,434	---	Yes	Yes	0,224	---	Yes	Yes	0,494	---	No	No	0,191	---	No	No
		Year 2013	0,299	---	No	No	0,448	---	Yes	Yes	0,247	---	No	Yes	N/A (product launched in 2013)				0,149	---	No	No
		Year 2014	0,097	---	No	No	0,308	---	No	No	0,561	---	No	No	0,615	---	No	No	0,107	---	No	No
		Year 2015	0,428	---	No	No	0,739	---	No	No	0,812	---	No	No	1,385	---	No	No	0,299	---	No	No
Adjusted R^2			0,744				0,699				0,836				0,961				0,136			
ANOVA Sig.			0,000				0,000				0,000				0,000				0,281			

Table 10.70 – Summary of Model 7 – Market 3 - Heart

Model specification			Model 7																	
			Product HE1				Product HE2				Product HE3				Product HE4				Product HE5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			30,257	---	Yes	Yes	18,052	---	Yes	Yes	19,092	---	No	No	22,341	---	Yes	Yes	0,318	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,720	No	Yes	Yes	-0,322	No	Yes	Yes	-0,976	No	No	No	-0,065	No	No	No	0,030	Yes	No	No
	Ln Sales in DDDs lagged two periods		-0,297	No	No	No	0,173	Yes	No	No	0,876	Yes	No	No	0,187	Yes	No	No	0,011	Yes	No	No
Marketing expenditures flow	Own	Ln Detailing flow	0,039	Yes	No	No	0,201	Yes	No	No	-0,719	No	No	No	0,202	Yes	No	Yes	0,302	Yes	No	No
		Ln Journal advertising flow	-0,003	No	No	No	0,005	Yes	Yes	Yes	No investments in time series				No investments in time series				0,007	Yes	No	No
		Ln Direct marketing flow	-0,006	No	No	No	-0,010	No	Yes	Yes	-0,002	No	No	No	No investments in time series				0,003	Yes	No	No
	Competitive	Ln Competitive marketing expenditures flow	-0,073	Yes	No	Yes	-0,044	Yes	No	No	-0,086	Yes	No	No	-0,041	Yes	No	No	-0,039	Yes	No	No
Marketing expenditures stock	Own	Ln Detailing stock	0,087	Yes	No	Yes	-0,117	No	No	No	-0,219	No	No	No	0,745	Yes	No	Yes	0,119	Yes	No	No
		Ln Other marketing expenditures stock	0,011	Yes	No	No	0,064	Yes	Yes	Yes	0,023	Yes	No	No	0,004	Yes	No	No	-0,010	No	No	No
	Competitive	Ln Competitive global marketing expenditures stock	0,041	No	No	No	-0,059	Yes	No	No	0,427	No	No	No	-0,384	Yes	Yes	Yes	0,234	No	No	No
Price	Own	Ln Average drug price per DDD	3,074	No	No	No	-0,058	Yes	No	No	5,711	No	No	No	-1,595	Yes	No	No	-3,529	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	0,152	Yes	No	No	-0,264	No	No	No	-9,885	No	No	No	-1,931	No	No	Yes	-2,393	No	No	No
Drug age		Drug age	0,024	Yes	No	No	-0,009	No	No	No	-0,048	No	No	No	-0,048	No	Yes	Yes	0,135	Yes	Yes	Yes
		Drug age squared	-0,0002	Yes	No	No	-0,0002	Yes	No	Yes	Removed due to multicollinearity				Removed due to multicollinearity				-0,001	Yes	Yes	Yes
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		Removed due to multicollinearity				0,168	Yes	No	No	-0,456	No	No	No	0,153	Yes	No	Yes	0,280	Yes	No	No
	Ln Average drug price per DDD x Ln Detailing stock		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				0,523	Yes	No	Yes	Removed due to multicollinearity			
	Ln Average drug price per DDD x Drug age		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				0,027	No	No	No
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				0,063	No	No	No	Removed due to multicollinearity			
Policy change	Loss of exclusivity		N/A				N/A				-0,388	Yes	No	No	-0,166	Yes	Yes	Yes	N/A			
Additional variables	Ipad / Tablet (% of times used in calls)		0,097	---	No	No	0,362	---	No	Yes	0,027	---	No	No	Missing information				-0,520	---	No	No
	Laptop based materials (% of times used in calls)		0,175	---	No	No	-1,032	---	No	No	Missing information								-1,157	---	No	No
	Printed material (% of times used in calls)		0,047	---	No	No	0,098	---	No	No	0,057	---	No	No					0,090	---	No	No
	Very useful (% of calls)		-0,071	---	No	No	0,110	---	No	No	0,091	---	No	No					0,315	---	No	No
	Increase / Will begin to prescribe (% of calls)		0,001	---	No	No	0,028	---	No	No	-0,029	---	No	No					0,119	---	No	No
	Ln Avg number of products presented during the calls		0,090	---	No	No	-0,023	---	No	No	-0,032	---	No	No					0,280	---	No	No
Temporal dummies		Quarter 2	0,095	---	Yes	Yes	0,189	---	Yes	Yes	0,252	---	No	No	0,082	---	No	No	0,025	---	No	No
		Quarter 3	0,162	---	Yes	Yes	0,259	---	Yes	Yes	0,117	---	No	No	0,138	---	No	No	0,027	---	No	No
		Quarter 4	0,236	---	Yes	Yes	0,428	---	Yes	Yes	0,408	---	No	No	0,266	---	Yes	Yes	0,166	---	No	No
		Year 2013	0,246	---	No	Yes	0,506	---	Yes	Yes	0,898	---	No	No	0,152	---	No	No	N/A (product launched in 2013)			
		Year 2014	0,595	---	Yes	Yes	1,099	---	Yes	Yes	1,786	---	No	Yes	0,433	---	No	No	0,136	---	No	No
		Year 2015	0,922	---	Yes	Yes	1,870	---	Yes	Yes	1,327	---	No	No	0,728	---	No	No	0,209	---	No	No
Adjusted R^2			0,873				0,757				0,877				0,984				0,988			
ANOVA Sig.			0,000				0,000				0,021				0,000				0,000			

Table 10.71 – Summary of Model 7 – Market 4 - Liver

Model specification			Model 7																	
			Product LI1				Product LI2				Product LI3				Product LI4				Product LI5			
			Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?	Estimate	Expect. signal?	p<0.05?	p<0.10?
Constant			28,565	---	Yes	Yes	17,810	---	Yes	Yes	14,178	---	No	No	6,373	---	No	No	7,793	---	No	No
Lagged sales	Ln Sales in DDDs lagged one period		-0,499	No	Yes	Yes	-0,507	No	Yes	Yes	-0,547	No	Yes	Yes	-0,409	No	No	Yes	-0,089	No	No	No
	Ln Sales in DDDs lagged two periods		0,074	Yes	No	No	0,005	Yes	No	No	-0,138	No	No	No	0,113	Yes	No	No	0,278	Yes	No	No
Marketing expenditures flow	Own	Ln Detailing flow	-0,018	No	No	No	-0,001	No	No	No	0,832	Yes	No	No	0,062	Yes	No	No	-0,218	No	No	No
		Ln Journal advertising flow	0,001	Yes	No	No	0,001	Yes	No	No	0,008	Yes	Yes	Yes	-0,002	No	No	No	0,002	Yes	No	No
		Ln Direct marketing flow	-0,005	No	No	No	-0,004	No	No	No	0,006	Yes	No	No	-0,0001	No	No	No	-0,010	No	Yes	Yes
	Competitive	Ln Competitive marketing expenditures flow	0,075	No	No	No	-0,016	Yes	No	No	0,038	No	No	No	-0,076	Yes	No	No	0,071	No	No	No
Marketing expenditures stock	Own	Ln Detailing stock	-0,133	No	No	No	0,049	Yes	No	No	0,407	Yes	No	No	0,062	Yes	No	No	0,142	Yes	No	No
		Ln Other marketing expenditures stock	0,037	Yes	No	No	-0,014	No	No	No	0,066	Yes	Yes	Yes	0,023	Yes	No	No	-0,001	No	No	No
	Competitive	Ln Competitive global marketing expenditures stock	-0,185	Yes	No	No	0,161	No	No	No	-0,147	Yes	No	No	0,111	No	No	No	0,151	No	No	No
Price	Own	Ln Average drug price per DDD	-0,320	Yes	No	No	1,890	No	No	No	-13,774	Yes	No	No	-13,448	Yes	No	No	-5,500	Yes	No	No
	Competitors	Ln Average competitors drug price per DDD	1,777	Yes	No	No	0,486	Yes	No	No	-0,204	No	No	No	2,900	Yes	No	No	0,906	Yes	Yes	Yes
Drug age		Drug age	-0,058	No	No	No	-0,015	No	No	No	0,050	Yes	No	No	0,006	Yes	No	No	0,010	Yes	No	No
		Drug age squared	0,0001	No	No	No	-0,0001	Yes	No	No	-0,0003	Yes	Yes	Yes	-0,0002	Yes	No	No	-0,0004	Yes	No	No
Marketing expenditures interactions	Ln Average drug price per DDD x Ln Detailing flow		Removed due to multicollinearity				Removed due to multicollinearity				1,578	Yes	No	No	Removed due to multicollinearity				0,460	Yes	0,551	
	Ln Average drug price per DDD x Ln Detailing stock		Removed due to multicollinearity				Removed due to multicollinearity				0,355	Yes	No	No	Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Average drug price per DDD x Drug age		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity			
	Ln Global marketing expenditures stock x Ln Average competitors price per DDD		Removed due to multicollinearity				Removed due to multicollinearity				Removed due to multicollinearity				-0,213	Yes	No	No	Removed due to multicollinearity			
Additional variables	Ipad / Tablet (% of times used in calls)		0,003	---	No	No	0,276	---	No	No	0,134	---	No	No	0,065	---	No	No	0,016	---	No	No
	Laptop based materials (% of times used in calls)		0,882	---	No	No	0,127	---	No	No	0,064	---	No	No	-0,402	---	No	No	-0,389	---	No	No
	Printed material (% of times used in calls)		-0,068	---	No	No	0,084	---	No	No	-0,175	---	Yes	Yes	0,124	---	No	No	0,154	---	No	No
	Very useful (% of calls)		0,088	---	No	No	0,010	---	No	No	-0,177	---	No	Yes	-0,208	---	No	No	-0,271	---	No	No
	Increase / Will begin to prescribe (% of calls)		0,184	---	No	No	-0,054	---	No	No	0,216	---	Yes	Yes	-0,011	---	No	No	0,135	---	No	No
	Ln Avg number of products presented during the calls		0,053	---	No	No	-0,072	---	No	No	0,176	---	Yes	Yes	0,172	---	No	No	-0,127	---	No	No
Temporal dummies	Quarter 2		0,111	---	No	No	0,142	---	Yes	Yes	0,047	---	No	No	0,125	---	Yes	Yes	0,189	---	Yes	Yes
	Quarter 3		0,250	---	No	Yes	0,240	---	Yes	Yes	0,173	---	Yes	Yes	0,169	---	Yes	Yes	0,268	---	Yes	Yes
	Quarter 4		0,298	---	No	No	0,380	---	Yes	Yes	0,207	---	Yes	Yes	0,290	---	Yes	Yes	0,425	---	Yes	Yes
	Year 2013		0,233	---	No	No	0,528	---	Yes	Yes	0,207	---	No	No	0,385	---	Yes	Yes	0,533	---	Yes	Yes
	Year 2014		0,703	---	No	No	0,983	---	Yes	Yes	0,545	---	Yes	Yes	0,700	---	Yes	Yes	1,033	---	Yes	Yes
	Year 2015		1,105	---	No	No	1,443	---	Yes	Yes	0,887	---	Yes	Yes	1,123	---	Yes	Yes	1,499	---	Yes	Yes
Adjusted R^2			0,148				0,483				0,667				0,941				0,779			
ANOVA Sig.			0,253				0,001				0,001				0,000				0,000			

10.5.4.2. Results

Based on the four tables shown above, we prepared a summary of results for a better interpretation (table 10.72).

Table 10.72 – Summary of Model 7 results

	Market 1 - Blood (3 products)				Market 2 - Pancreas (5 products)				Market 3 - Heart (5 products)				Market 4 - Liver (5 products)				Global (18 products)			
	% cases with…		Average elasticities		% cases with…		Average elasticities		% cases with…		Average elasticities		% cases with…		Average elasticities		% cases with…		Average elasticities	
	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.	Exp. signal	Exp. signal and p<0.05	All cases	When signal is as exp.
Ln Sales in DDDs lagged one period	66,7%	0,0%	0,062	0,297	0,0%	0,0%	-0,478	N/A	20,0%	0,0%	-0,411	0,030	0,0%	0,0%	-0,410	N/A	16,7%	0,0%	-0,351	0,163
Ln Sales in DDDs lagged two periods	50,0%	50,0%	0,217	0,440	20,0%	0,0%	-0,043	0,105	80,0%	0,0%	0,190	0,312	80,0%	0,0%	0,066	0,117	58,8%	5,9%	0,088	0,215
Ln Detailing flow	100,0%	0,0%	0,118	0,118	60,0%	0,0%	0,166	0,334	80,0%	0,0%	0,005	0,186	40,0%	0,0%	0,131	0,447	66,7%	0,0%	0,103	0,249
Ln Journal advertising flow	100,0%	0,0%	0,007	0,007	60,0%	20,0%	0,000	0,004	66,7%	33,3%	0,003	0,006	80,0%	20,0%	0,002	0,003	75,0%	18,8%	0,002	0,005
Ln Direct marketing flow	33,3%	0,0%	-0,001	0,008	60,0%	0,0%	0,002	0,006	25,0%	0,0%	-0,004	0,003	20,0%	0,0%	-0,003	0,006	35,3%	0,0%	-0,001	0,006
Ln Competitive marketing expenditures flow	33,3%	0,0%	-0,020	-0,158	20,0%	0,0%	-0,001	-0,124	100,0%	0,0%	-0,056	-0,056	40,0%	0,0%	0,019	-0,046	50,0%	0,0%	-0,014	-0,073
Ln Detailing stock	100,0%	0,0%	0,275	0,275	80,0%	0,0%	0,342	0,478	60,0%	0,0%	0,123	0,317	80,0%	0,0%	0,106	0,165	77,8%	0,0%	0,204	0,311
Ln Other marketing expenditures stock	33,3%	0,0%	0,033	0,249	60,0%	0,0%	0,004	0,029	80,0%	20,0%	0,018	0,026	60,0%	20,0%	0,022	0,042	61,1%	11,1%	0,018	0,051
Ln Competitive global marketing expenditures stock	50,0%	0,0%	0,028	-0,022	40,0%	0,0%	0,238	-0,098	40,0%	20,0%	0,052	-0,222	40,0%	0,0%	0,018	-0,166	41,2%	5,9%	0,094	-0,142
Ln Average drug price per DDD	33,3%	0,0%	0,639	-0,743	75,0%	0,0%	-4,941	-8,621	60,0%	0,0%	0,721	-1,727	80,0%	0,0%	-6,230	-8,260	64,7%	0,0%	-2,670	-5,893
Ln Average competitors drug price per DDD	0,0%	0,0%	-0,84	N/A	40,0%	0,0%	-36,05	3,260	20,0%	0,0%	-2,864	0,152	80,0%	20,0%	1,173	1,517	41,2%	5,9%	-11,20	1,820
Drug age	66,7%	0,0%	0,051	0,087	40,0%	0,0%	0,012	0,087	40,0%	20,0%	0,011	0,080	60,0%	0,0%	-0,001	0,022	50,0%	5,6%	0,015	0,064
Drug age squared	N/A	N/A	N/A	N/A	100,0%	20,0%	-0,0002	-0,0002	100,0%	33,3%	-0,0005	-0,0005	80,0%	20,0%	-0,0002	-0,0003	92,3%	23,1%	-0,0003	-0,0003
Ln Average drug price per DDD x Ln Detailing flow	0,0%	0,0%	-0,126	N/A	25,0%	0,0%	-0,281	0,495	75,0%	0,0%	0,036	0,200	100,0%	0,0%	1,019	1,019	50,0%	0,0%	0,067	0,522
Ln Average drug price per DDD x Ln Detailing stock	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	100,0%	0,0%	0,523	0,523	100,0%	0,0%	0,355	0,355	100,0%	0,0%	0,439	0,439
Ln Average drug price per DDD x Drug age	100,0%	0,0%	-0,014	-0,014	0,0%	0,0%	0,228	N/A	0,0%	0,0%	0,027	N/A	N/A	N/A	N/A	N/A	33,3%	0,0%	0,080	-0,014
Ln Global marketing expenditures stock x Ln Average competitors price per DDD	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0,0%	0,0%	0,063	N/A	100,0%	0,0%	-0,213	-0,213	50,0%	0,0%	-0,075	-0,213
Public reimbursement	66,7%	33,3%	1,537	2,409	---	---	---	---	---	---	---	---	---	---	---	---	66,7%	33,3%	1,537	2,409
Loss of exclusivity	---	---	---	---	---	---	---	---	100,0%	50,0%	-0,277	-0,277	---	---	---	---	100,0%	50,0%	-0,277	-0,277
Ipad / Tablet (% of times used in calls)	---	---	0,156	---	---	---	0,046	---	---	---	-0,009	---	---	---	0,099	---	---	---	0,068	---
Laptop based materials (% of times used in calls)	---	---	-0,741	---	---	---	0,218	---	---	---	-0,671	---	---	---	0,056	---	---	---	-0,179	---
Printed material (% of times used in calls)	---	---	0,050	---	---	---	0,016	---	---	---	0,073	---	---	---	0,024	---	---	---	0,038	---
Very useful (% of calls)	---	---	-0,182	---	---	---	0,035	---	---	---	0,111	---	---	---	-0,112	---	---	---	-0,028	---
Increase / Will begin to prescribe (% of calls)	---	---	0,041	---	---	---	-0,099	---	---	---	0,030	---	---	---	0,094	---	---	---	0,013	---
Ln Avg number of products presented during the calls	---	---	0,063	---	---	---	-0,256	---	---	---	0,079	---	---	---	0,041	---	---	---	-0,034	---

10.5.5. Comparative analysis of Models 5 to 7

In order to compare the additional models (5 to 7) fit we calculated AIC and BIC.

The next tables (10.73, 10.74 and 10.75) evidence the AICs and BICs for all the products, for each of the three additional models (5 to 7).

Table 10.73 – AICs and BICs for model 5

		Model 5																	
		Market 1 - Blood			Market 2 - Pancreas					Market 3 - Heart					Market 4 - Liver				
		BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5	
	n	48	48	18	48	48	48	33	48	48	48	48	35	48	48	48	48	48	48	
	SSR	0,17	0,08	0,00	0,05	0,04	0,04	0,34	0,06	0,04	0,04	0,12	0,10	0,05	0,16	0,07	0,06	0,07	0,09	
	k	22	23	17	22	21	21	19	21	21	22	22	21	21	20	21	22	21	21	
AIC	AIC	-227,7	-263,0	-161,7	-290,0	-303,1	-298,3	-113,4	-276,8	-299,3	-300,8	-242,3	-163,6	-285,1	-232,8	-273,5	-273,4	-271,3	-258,3	All products
	AIC mean	-217,5			-256,3					-258,2					-261,9					-251,9
	AIC SD	51,4			80,5					57,9					17,4					54,3
BIC	BIC	-186,5	-220,0	-146,6	-248,8	-263,8	-259,0	-84,9	-237,5	-260,0	-259,6	-201,1	-131,0	-245,8	-195,4	-234,2	-232,2	-232,0	-219,0	All products
	BIC mean	-184,4			-218,8					-219,5					-222,6					-214,3
	BIC SD	36,7			75,5					55,0					16,4					49,7

Source: own elaboration

Table 10.74 – AICs and BICs for model 6

		Model 6																	
		Market 1 - Blood			Market 2 - Pancreas					Market 3 - Heart					Market 4 - Liver				
		BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5
	n	48	48	18	48	48	48	33	48	48	48	48	35	48	48	48	48	48	48
	SSR	0,17	0,10	0,00	0,06	0,05	0,04	0,30	0,07	0,04	0,05	0,06	0,11	0,03	0,15	0,06	0,08	0,05	0,09
	k	24	24	18	23	23	23	23	23	23	23	23	18	22	23	23	23	23	23
AIC	AIC	-223,7	-246,5	-601,0	-275,2	-285,4	-295,6	-108,6	-268,8	-292,7	-279,6	-277,0	-164,6	-303,8	-229,3	-273,1	-264,0	-281,3	-253,6	All products
AIC	AIC mean	-357,1			-246,7					-263,5					-260,3					-273,5
AIC	AIC SD	211,6			77,9					56,4					20,2					95,2
BIC	BIC	-178,8	-201,6	-585,0	-232,1	-242,4	-252,6	-74,2	-225,7	-249,6	-236,5	-234,0	-136,6	-262,6	-186,3	-230,1	-221,0	-238,3	-210,5	All products
BIC	BIC mean	-321,8			-205,4					-223,9					-217,2					-233,2
BIC	BIC SD	228,2			74,1					50,1					20,2					99,1

Table 10.75 – AICs and BICs for model 7

		Model 7																	
		Market 1 - Blood			Market 2 - Pancreas					Market 3 - Heart					Market 4 - Liver				
		BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5
	n	48	48	18	48	48	48	33	48	48	48	48	35	48	48	48	48	48	48
	SSR	0,14	0,10	0,00	0,04	0,03	0,03	0,23	0,06	0,04	0,03	0,03	0,10	0,03	0,14	0,06	0,03	0,06	0,07
	k	28	27	17	28	27	27	24	27	26	27	25	21	27	26	26	28	27	27
AIC	AIC	-225,7	-244,8	N/A	-287,6	-293,9	-298,2	-116,0	-264,3	-293,5	-308,2	-312,1	-163,6	-303,6	-226,8	-268,3	-291,2	-270,8	-261,2	All products
AIC	AIC mean	-235,2			-252,0					-276,2					-263,6					-260,6
AIC	AIC SD	13,5			77,2					63,3					23,4					53,1
BIC	BIC	-173,3	-194,2	N/A	-235,2	-243,4	-247,6	-80,1	-213,8	-244,8	-257,7	-265,3	-131,0	-253,1	-178,2	-219,6	-238,8	-220,3	-210,6	All products
BIC	BIC mean	-183,8			-204,0					-230,4					-213,5					-212,2
BIC	BIC SD	14,8			70,5					56,1					22,2					48,9

Table 10.76 below summarizes the average AICs and BICs per market.

Table 10.76 – Summary of average AICs and BICs per market and model (1 to 7)

		Summary				
		Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Average AIC	Model 1 (Wittink 2002 simplified)	-183,0	-238,0	-220,8	-252,7	-228,1
	Model 2 (Wittink 2002 complete)	-189,1	-235,9	-222,2	-251,9	-228,7
	Model 3 (Rizzo 1999)	-173,8	-240,4	-229,0	-248,4	-228,3
	Model 4 (Winmeijer et al 2006)	-187,9	-250,8	-251,8	-262,5	-243,8
	Model 5	-217,5	-256,3	-258,2	-261,9	-251,9
	Model 6	-357,1	-246,7	-263,5	-260,3	-273,5
	Model 7	-235,2	-252,0	-276,2	-263,6	-260,6

		Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Average BIC	Model 1 (Wittink 2002 simplified)	-160,5	-212,9	-196,1	-226,8	-203,4
	Model 2 (Wittink 2002 complete)	-160,9	-204,1	-192,4	-219,3	-197,9
	Model 3 (Rizzo 1999)	-154,9	-220,0	-208,1	-227,8	-208,0
	Model 4 (Winmeijer et al 2006)	-160,3	-221,2	-220,0	-230,6	-213,3
	Model 5	-184,4	-218,8	-219,5	-222,6	-214,3
	Model 6	-321,8	-205,4	-223,9	-217,2	-233,2
	Model 7	-183,8	-204,0	-230,4	-213,5	-212,2

Source: own elaboration

Figure 10.131 below presents the same information in a chart format.

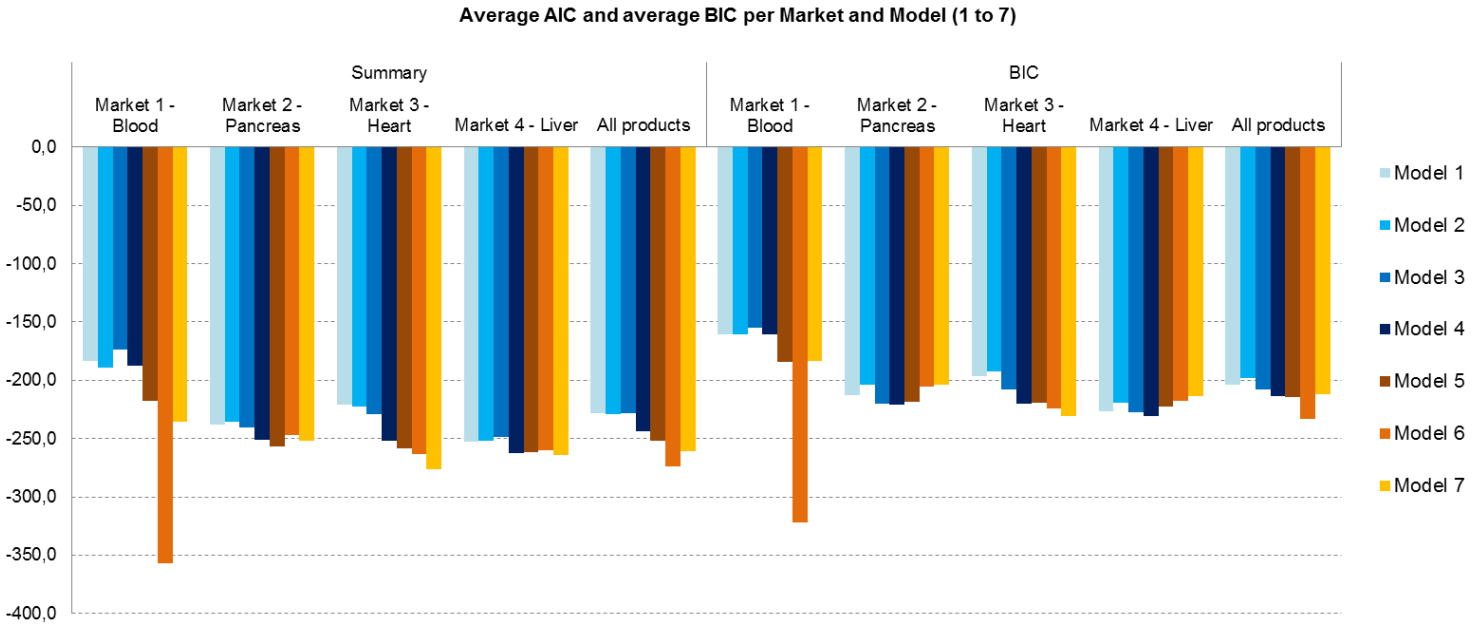


Figure 10.131 – Average AIC and average BIC per Market and Model (1 to 7)

Source: own elaboration

Model 6 evidences the lower average AICs and BICs. In order to allow additional insights, we calculated the relative likelihood (Burnham & Anderson, 2003) of Models 5 and 7 against Model 6.

Table 10.77 shows the AIC relative likelihood among markets, in Models 5 and 7 versus Model 6.

Table 10.77 – AIC relative likelihood among markets – Models 5 and 7 versus Model 6

	Times as probable as model 6 to minimize information loss				
	Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Model 5	0,0000	123,0044	0,0707	2,2247	0,0000
Model 7	0,0000	14,0270	571,8052	5,4255	0,0015

Model 6 stands out as the one with the global higher fit. However, Model 7 has a better fit than Model 6 in three of the four markets.

Table 10.78 below presents the AIC variation of Models 5 and 7 versus Model 6.

Table 10.78 – Variation of AIC of Models 5 and 7 against Model 6

	Variation of AIC of each model versus Model 6				
	Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Model 5	139,6	-9,6	5,3	-1,6	21,6
Model 7	121,8	-5,3	-12,7	-3,4	13,0

Again, model 6 evidences the highest global fit, but loses to Model 7 in three out of four markets.

Table 10.79 below highlights the delta of Models 5 and 7 BICs against Model 6 BICs.

Table 10.79 – Variation of BIC of Models 5 and 7 against Model 6

	Variation of BIC of each model versus Model 6				
	Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	All products
Model 5	137,4	-13,4	4,4	-5,3	18,9
Model 7	138,0	1,4	-6,5	3,7	21,0

As a conclusion, there is sufficient evidence to consider Model 6 as globally the most suited for the type of data we used. However, there are two main important aspects to address, which will impact the final choice of the model to use:

- Model 6 AIC is only better than Model 7 AIC due to the fact that the SSR in product BL3 in Model 7 equals zero (0,000). This way, the AIC calculation was not possible, provoking an "artificial" increase (in the positive direction) on the AIC average for market 1 – Blood. Should SSR be marginally higher than zero and Model 7 would be the one with the lowest AIC

- Our thesis is directed at studying the effect, on detailing elasticities, of the entry into force of a detailing ceiling. This means that Model 6 must not be the one selected, as it does not include the variable Ln Detailing flow (it only includes Ln Global marketing expenditures flow)

Given the two reasons described above, we selected model 7 as the basis to the next steps of our thesis.

Before moving to the analysis of structural breaks in our data (with future model 8.4), we performed additional analysis with Model 7. In order to allow deeper insights and discussion of its results against the theory, and also having the goal of finding patterns for younger or older drugs, we performed a very simple analysis: instead of defining an arbitrary threshold above which a drug would be considered as older (in opposition to younger), we:

- Calculated drug age for each of the 18 products (number of months that have passed since product started its commercialization in the market). The reference month was the last observation (December 2015), so if a drug was launched on January 2015 its age would be 12 months on December 2015;

- Calculated the median of drug age, which resulted in a value of 84

- Classified all products as Younger or Older, using the reference value of 84

We then built table 10.80 highlighting a series of results for each of the 18 products.

Table 10.80 – Classification of products as Younger or Older – Model 7

	Product																	
	BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5
	Older	Younger	Younger	Older	Older	Younger	Younger	Younger	Older	Older	Older	Older	Younger	Older	Older	Older	Younger	Younger
Drug age at the end of the time series	84	81	47	84	88	75	47	75	102	87	197	193	47	141	128	139	54	61
Detailing flow elasticity	0,012	0,214	0,127	0,061	-0,125	-0,049	0,597	0,344	0,039	0,201	-0,719	0,202	0,302	-0,018	-0,001	0,832	0,062	-0,218
Journal advertising flow elasticity	0,007	0,005	0,008	-0,006	0,006	0,004	-0,006	0,003	-0,003	0,005	---	---	0,007	0,001	0,001	0,008	-0,002	0,002
Direct marketing (mailing) flow elasticity	0,008	-0,002	-0,009	-0,005	0,001	0,000	0,015	-0,002	-0,006	-0,010	-0,002	---	0,003	-0,005	-0,004	0,006	0,000	-0,010
Detailing stock elasticity	0,334	0,139	0,353	0,037	-0,203	0,049	1,728	0,099	0,087	-0,117	-0,219	0,745	0,119	-0,133	0,049	0,407	0,062	0,142
Average drug price per DDD x Ln Detailing flow elasticity	-0,008	-0,244	---	-0,332	0,495	-0,301	---	-0,986	---	0,168	-0,456	0,153	0,280	---	---	1,578	---	0,460
Ipad / Tablet (% of times used in calls)	-0,031	0,345	0,153	0,285	0,043	-0,394	0,295	0,004	0,097	0,362	0,027	---	-0,520	0,003	0,276	0,134	0,065	0,016
Laptop based materials (% of times used in calls)	0,727	-1,548	-1,403	0,040	-0,002	-0,130	0,998	0,182	0,175	-1,032	---	---	-1,157	0,882	0,127	0,064	-0,402	-0,389
Printed material (% of times used in calls)	0,289	0,205	-0,345	0,002	0,064	0,044	-0,021	-0,011	0,047	0,098	0,057	---	0,090	-0,068	0,084	-0,175	0,124	0,154
Very useful (% of calls)	-0,091	-0,147	-0,308	-0,196	-0,140	0,147	0,338	0,027	-0,071	0,110	0,091	---	0,315	0,088	0,010	-0,177	-0,208	-0,271
Increase / Will begin to prescribe (% of calls)	-0,031	0,036	0,117	0,156	0,050	-0,055	-0,636	-0,012	0,001	0,028	-0,029	---	0,119	0,184	-0,054	0,216	-0,011	0,135
Avg number of products presented during the calls elasticity	-0,362	-0,146	0,698	0,076	-0,101	-0,120	-1,084	-0,050	0,090	-0,023	-0,032	---	0,280	0,053	-0,072	0,176	0,172	-0,127

Source: own elaboration

Table 10.80 also evidences the average results of the variable coefficients.

We then calculated the averages of some of these variables, here shown below in table 10.81, in columns 3 and 4.

Table 10.81 – Average coefficient results for drugs – Model 7

	Percentile 50% as a cut point		Quartiles 1 and 3 as cut points	
	Younger	Older	Much Younger	Much Older
	(n=8)	(n=10)	(n=5)	(n=5)
Detailing flow elasticity	0,172	0,048	0,174	0,059
Journal advertising flow elasticity	0,003	0,002	0,002	0,003
Direct marketing (mailing) flow elasticity	0,000	-0,002	0,000	-0,002
Detailing stock elasticity	0,336	0,099	0,481	0,170
Average drug price per DDD x Ln Detailing flow elasticity	-0,158	0,228	0,370	0,425
Ipad / Tablet (% of times used in calls)	-0,005	0,133	0,002	0,110
Laptop based materials (% of times used in calls)	-0,481	0,123	-0,471	0,358
Printed material (% of times used in calls)	0,030	0,044	0,001	-0,025
Very useful (% of calls)	-0,013	-0,042	-0,027	0,003
Increase / Will begin to prescribe (% of calls)	-0,038	0,058	-0,055	0,079
Avg number of products presented during the calls	-0,047	-0,022	-0,012	0,032

Source: own elaboration

Some very interesting patterns started to appear. But in order to allow even higher evidence, we performed the exact same analysis using quartile 1 (percentiles ≤ 25%, cut point at 64,5 months) and quartile 3 (percentile ≥ 75%, cut point at 121,5 months) as references. The results are shown above, in columns 4 and 5 of table 10.81.

10.6. Additional models

After applying seven models to our data, we chose, as addressed before, Model 7 as globally the most appropriate. As discussed previously, Model 7 does evidence most of the coefficients as non-significant, such as seen in Windmeijer et al (2006) and Leeflang & Wieringa (2010). In order to try to find additional patterns in our data, we decided to test other models:

- Model 8.1 – consists of the full Model 7, but this time manually removing, step by step, all the non-significant variables (removing the ones with the highest p-values first)

- Model 8.2 – consists of the full Model 7, but with stepwise regression, leaving SPSS to select the significant variables
- Model 8.3 - A first attempt to build a final model, with a limited number of selected independent variables

Our goal was to see which significant variables would remain, and which patterns would appear, to help us generalize.

10.6.1. Model 8.1 - Model 7 with manual non-significant variables removal

10.6.1.1. Procedures and outputs

We started by selecting pairs of products, chosing product BL3 from Market 1 (younger product, launched in the market in July 2014, and product HE3, an older product (launched in the early years of the 21st century). In each iteration, in SPSS, we used a second block with all the variables from Model 7, and activated the option R^2 change.

H_0: $R^2_u = R^2$

H_a: $R^2_u \neq R^2$

If the variable removed in each iteration generates a R^2 change higher than 0,05, therefore we do not reject the hypothesis that the R^2 are considered equal.

We present an example of the first two iterations, for product HE3, using exactly the same initial variables as in Model 7 (also excluding the variables that were provoking multicollinearity). The output is shown below in figure 10.132.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	19,092	12,458		1,532	,200
	Ln Sales in DDDs lagged one period	-,976	,591	-,854	-1,652	,174
	Ln Sales in DDDs lagged two periods	,876	,692	,790	1,266	,274
	Ln Detailing flow (calls)	-,719	,668	-4,195	-1,077	,342
	Ln Mailing flow	-,002	,029	-,022	-,075	,944
	Ln Competitive global marketing expenditures flow	-,086	,189	-,105	-,456	,672
	Ln Detailing stock (calls)	-,219	,185	-1,067	-1,187	,301
	Ln Other marketing expenditures stock	,023	,022	,248	1,065	,347
	Ln Competitive global marketing expenditures stock	,427	,675	,305	,632	,562
	Ln Average drug price per DDD	5,711	3,533	4,305	1,616	,181
	Ln Average competitors price per DDD	-9,885	5,892	-1,368	-1,678	,169
	Drug age	-,048	,028	-2,337	-1,679	,168
	Ln Drug price x Ln Detailing flow	-,456	,476	-3,207	-,959	,392
	Loss of exclusivity (dummy)	-,388	,183	-,705	-2,119	,101
	Ipad / Tablet (% of times used in calls)	,027	,150	,031	,179	,867
	Printed material (% of times used in calls)	,057	,147	,092	,390	,717
	Very useful (% of calls)	,091	,126	,158	,722	,510
	Increase / Will begin to prescribe (% of calls)	-,029	,216	-,050	-,136	,899
	Ln Avg number of products presented during the calls	-,032	,102	-,059	-,311	,771
	Quarter 2 (dummy)	,252	,225	,484	1,123	,324
	Quarter 3 (dummy)	,117	,243	,224	,481	,655
	Quarter 4 (dummy)	,408	,314	,690	1,300	,263
	Year 2013 (dummy)	,898	,433	1,862	2,072	,107
	Year 2014 (dummy)	1,786	,833	3,242	2,144	,099
	Year 2015 (dummy)	1,327	1,352	1,507	,982	,382

a. Dependent Variable: Ln Sales in DDDs

Figure 10.132 – Outputs of product HE3 in Model 8.1 – first iteration

The variable Ln Mailing flow has the highest sig (last column of the table above, 0,944, in figure 10.133), so it was the first variable to remove.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	,991[a]	,982	,901	,071333644	,982	12,123	23	5	,006
2	,991[b]	,982	,877	,079697803	,000	,006	1	4	,944

a. Predictors: (Constant), Year 2015 (dummy), Ln Detailing flow (calls), Ln Other marketing expenditures stock, Quarter 2 (dummy), Year 2014 (dummy), Increase / Will begin to prescribe (% of calls), Quarter 4 (dummy), Printed material (% of times used in calls), Ipad / Tablet (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Avg number of products presented during the calls, Year 2013 (dummy), Very useful (% of calls), Quarter 3 (dummy), Ln Average competitors price per DDD, Ln Competitive global marketing expenditures stock, Loss of exclusivity (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Detailing stock (calls), Drug age, Ln Average drug price per DDD, Ln Drug price x Ln Detailing flow

b. Predictors: (Constant), Year 2015 (dummy), Ln Detailing flow (calls), Ln Other marketing expenditures stock, Quarter 2 (dummy), Year 2014 (dummy), Increase / Will begin to prescribe (% of calls), Quarter 4 (dummy), Printed material (% of times used in calls), Ipad / Tablet (% of times used in calls), Ln Competitive global marketing expenditures flow, Ln Avg number of products presented during the calls, Year 2013 (dummy), Very useful (% of calls), Quarter 3 (dummy), Ln Average competitors price per DDD, Ln Competitive global marketing expenditures stock, Loss of exclusivity (dummy), Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period, Ln Detailing stock (calls), Drug age, Ln Average drug price per DDD, Ln Drug price x Ln Detailing flow, Ln Mailing flow

Figure 10.133 – R^2 change in the first iteration of product HE3 in Model 8.1

With an R^2 change of 0,944, we do not reject the hypothesis that the two R^2 are equal, and therefore we continued our analysis, removing variable after variable, with the following sequence:

- Increase / Will begin to prescribe (% of calls)
- Ipad / Tablet (% of times used in calls)
- Ln Avg number of products presented during the calls
- Ln Competitive global marketing expenditures flow
- Printed material (% of times used in calls)
- Very useful (% of calls)
- Ln Competitive global marketing expenditures stock
- Ln Detailing stock (calls)
- Ln Sales in DDDs lagged one period
- Ln Drug price x Ln Detailing flow
- Ln Detailing flow (calls)
- Ln Average drug price per DDD
- Ln Average competitors price per DDD
- Ln Other marketing expenditures stock

We then reached a final model including significant variables only, here shown below in figure 10.134.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	,966[a]	,932	,900	,071703298	,932	29,102	9	19	,000
2	,991[b]	,982	,877	,079697803	,050	,759	15	4	,692

a. Predictors: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Year 2013 (dummy), Quarter 3 (dummy), Year 2014 (dummy), Quarter 2 (dummy), Loss of exclusivity (dummy), Ln Sales in DDDs lagged two periods, Drug age

b. Predictors: (Constant), Year 2015 (dummy), Quarter 4 (dummy), Year 2013 (dummy), Quarter 3 (dummy), Year 2014 (dummy), Quarter 2 (dummy), Loss of exclusivity (dummy), Ln Sales in DDDs lagged two periods, Drug age, Ln Avg number of products presented during the calls, Printed material (% of times used in calls), Ln Competitive global marketing expenditures stock, Ipad / Tablet (% of times used in calls), Very useful (% of calls), Ln Competitive global marketing expenditures flow, Ln Drug price x Ln Detailing flow, Ln Other marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Ln Average competitors price per DDD, Ln Mailing flow, Ln Sales in DDDs lagged one period, Ln Detailing stock (calls), Ln Average drug price per DDD, Ln Detailing flow (calls)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	12,144	3,900		3,114	,006
	Ln Sales in DDDs lagged two periods	,717	,208	,647	3,444	,003
	Drug age	-,052	,019	-2,540	-2,747	,013
	Loss of exclusivity (dummy)	-,221	,070	-,400	-3,160	,005
	Quarter 2 (dummy)	,238	,069	,457	3,459	,003
	Quarter 3 (dummy)	,301	,114	,578	2,632	,016
	Quarter 4 (dummy)	,538	,174	,911	3,095	,006
	Year 2013 (dummy)	,630	,226	1,306	2,792	,012
	Year 2014 (dummy)	1,311	,450	2,380	2,911	,009
	Year 2015 (dummy)	1,859	,707	2,111	2,628	,017

a. Dependent Variable: Ln Sales in DDDs

Figure 10.134– Significant variables for product HE3 in Model 8.1

Interestingly, with the exception of the lagged variable (two periods) and Drug age (which has a negative coefficient, given that product HE3 has been declining its sales, very slowly though), all the significant variables are dummy (temporal dummies mostly, and loss of exclusivity).

We then moved to product BL3. After many iterations, we reached the final model, shown below (figure 10.135):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-3,778	,471		-8,030	,000
	Ln Other marketing expenditures stock	,413	,039	,201	10,486	,000
	Drug age	,154	,009	,408	17,830	,000
	Public reimbursement (dummy)	4,762	,169	,556	28,108	,000
	Year 2015 (dummy)	,324	,093	,078	3,480	,004

a. Dependent Variable: Ln Sales in DDDs

Figure 10.135 – Significant variables for product BL3 in Model 8.1

Only four variables were significant. In this case, given that product BL3 is very recent and is experiencing the initial stage of the product life cycle, Drug age coefficient expectedly has a positive signal. This product was clearly benefited by the public reimbursement.

In order to search for patterns, we extended our analysis to another pair of products: BL1 (at the end of the faster initial sales growth) and PA4 (substantially more recent), whose outputs are shown below in figure 10.136.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	6,775	1,078		6,286	,000
	Ln Sales in DDDs lagged one period	,373	,093	,375	4,018	,000
	Ln Average competitors price per DDD	-1,659	,399	-,145	-4,160	,000
	Drug age	,031	,007	,297	4,342	,000
	Public reimbursement (dummy)	,501	,064	,167	7,810	,000
	Printed material (% of times used in calls)	,213	,084	,021	2,530	,015
	Quarter 4 (dummy)	,071	,032	,022	2,253	,030
	Year 2015 (dummy)	,185	,070	,056	2,632	,012

a. Dependent Variable: Ln Sales in DDDs

Figure 10.136 – Significant variables for product BL1 in Model 8.1

Contrarily to the first pair of products, product BL1 has mainly non-dummy significant variables. The most intriguing one is Ln Average competitors' price per DDD, which has a negative signal, contrarily to what would be expected.

The significant variables in the case of product PA4 were the following (figure 10.137):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	47,558	11,007		4,321	,000
	Ln Detailing stock (calls)	,827	,097	,357	8,552	,000
	Ln Average competitors price per DDD	-229,155	54,164	-,200	-4,231	,000
	Drug age	,092	,003	1,099	27,335	,000
	Quarter 3 (dummy)	,175	,073	,097	2,389	,024
	Quarter 4 (dummy)	,176	,080	,098	2,197	,037

a. Dependent Variable: Ln Sales in DDDs

Figure 10.137 – Significant variables for product PA4 in Model 8.1

Detailing flow was not significant by a small value. The significant variables include two temporal dummies, drug age, average competitors price (whose coefficient is justified by the fast that prices in this market almost had no change at all, during the 48 months of our time series), and detailing stock.

In these two pairs of products we were not able, yet, to gain additional insights to help us generalize. Therefore, we decided to analyze all the remaining 14 products

In the case of product BL2, the significant variables were (figure 10.138):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	6,057	1,051		5,762	,000
	Ln Sales in DDDs lagged two periods	,485	,096	,551	5,037	,000
	Ln Competitive global marketing expenditures flow	,094	,038	,093	2,489	,018
	Drug age	-,031	,014	-,764	-2,196	,035
	Public reimbursement (dummy)	-,107	,047	-,092	-2,273	,029
	Ipad / Tablet (% of times used in calls)	,624	,273	,051	2,288	,028
	Laptop based materials (% of times used in calls)	-1,241	,351	-,070	-3,538	,001
	Printed material (% of times used in calls)	,276	,089	,075	3,090	,004
	Quarter 2 (dummy)	,114	,046	,089	2,486	,018
	Quarter 3 (dummy)	,256	,078	,199	3,292	,002
	Quarter 4 (dummy)	,475	,110	,368	4,310	,000
	Year 2013 (dummy)	,646	,143	,501	4,530	,000
	Year 2014 (dummy)	1,252	,285	,971	4,398	,000
	Year 2015 (dummy)	1,696	,437	1,315	3,879	,000

a. Dependent Variable: Ln Sales in DDDs

Figure 10.138 – Significant variables for product BL2 in Model 8.1

In the case of product BL2, 13 independent variables (approaximately half of the total) were significant, including the six dummy temporal variables. A very interesting conclusion in this product is that the use of printed materials and tablets during the calls appears to positively influence drug sales, whereas the use of laptop based materials appears to have a negative effect.

Moving to product PA1, the significant independent variables were the following (figure 10.139):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	32,040	2,478		12,929	,000
	Ln Sales in DDDs lagged one period	-,582	,108	-,579	-5,369	,000
	Ln Average competitors price per DDD	-28,340	4,035	-8,888	-7,024	,000
	Drug age	-,084	,013	-13,788	-6,586	,000
	Ln Drug price x drug age	,208	,031	5,817	6,743	,000
	Quarter 2 (dummy)	,135	,021	,691	6,550	,000
	Quarter 3 (dummy)	,241	,030	1,234	7,917	,000
	Quarter 4 (dummy)	,364	,044	1,863	8,301	,000
	Year 2013 (dummy)	,325	,045	1,663	7,174	,000
	Year 2015 (dummy)	,331	,052	1,695	6,315	,000

a. Dependent Variable: Ln Sales in DDDs

Figure 10.139 – Significant variables for product PA1 in Model 8.1

Nine independent variables coefficients were significant, including five dummy temporal variables.

We then moved to product PA2, whose significant variables are shown (figure 10.140):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	28,880	2,091		13,813	,000
	Ln Sales in DDDs lagged one period	-,506	,099	-,496	-5,132	,000
	Ln Journal advertising flow	,005	,002	,257	3,119	,004
	Ln Detailing stock (calls)	-,262	,080	-,910	-3,264	,002
	Ln Other marketing expenditures stock	,056	,026	,645	2,139	,040
	Ln Average drug price per DDD	-21,953	4,360	-7,402	-5,035	,000
	Ln Average competitors price per DDD	4,493	1,461	1,976	3,076	,004
	Drug age^2	,000	,000	-5,958	-5,121	,000
	Quarter 2 (dummy)	,090	,024	,538	3,744	,001
	Quarter 3 (dummy)	,242	,038	1,439	6,296	,000
	Quarter 4 (dummy)	,357	,056	2,126	6,407	,000
	Year 2013 (dummy)	,308	,064	1,836	4,822	,000
	Year 2015 (dummy)	,339	,062	2,022	5,476	,000

a. Dependent Variable: Ln Sales in DDDs

Figure 10.140 – Significant variables for product PA2 in Model 8.1

Twelve independent variables coefficients were significant, including five dummy temporal variables. Product PA2 is extremely sensitive to both changes in its own price, and changes in average competitors' price. Journal advertising has a marginal effect on drug sales (for each 1% change in journal advertising, drug sales in DDDs increase 0,005%.

Moving to product PA3, the variables with significant coefficients were (figure 10.141):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	17,612	1,943		9,065	,000
	Ln Sales in DDDs lagged one period	-,512	,121	-,541	-4,217	,000
	Ln Competitive global marketing expenditures flow	,149	,044	,385	3,407	,002
	Ln Average drug price per DDD	6,123	2,559	1,604	2,393	,022
	Drug age^2	,000	,000	-3,538	-4,985	,000
	Ln Drug price x Ln Detailing flow	-,432	,111	-,965	-3,896	,000
	Quarter 2 (dummy)	,161	,028	,739	5,831	,000
	Quarter 3 (dummy)	,264	,040	1,215	6,648	,000
	Quarter 4 (dummy)	,370	,053	1,699	6,944	,000
	Year 2013 (dummy)	,426	,069	1,958	6,216	,000
	Year 2014 (dummy)	,938	,179	4,309	5,246	,000
	Year 2015 (dummy)	1,377	,250	6,326	5,514	,000

a. Dependent Variable: Ln Sales in DDDs

Figure 10.141 – Significant variables for product PA3 in Model 8.1

Eleven independent variables coefficients were significant, including six dummy temporal variables. Product PA3 non-dummy variable coefficients the opposite signal as would be expected.

In the case of PA5, the variables with significant coefficients were (figure 10.142):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	11,664	2,142		5,445	,000
	Ln Sales in DDDs lagged one period	-,410	,138	-,400	-2,980	,005
	Ln Detailing flow (calls)	,174	,045	,977	3,838	,000
	Ln Competitive global marketing expenditures stock	,443	,134	1,283	3,298	,002
	Ln Drug price x Ln Detailing flow	-,432	,122	-1,247	-3,526	,001
	Quarter 3 (dummy)	,048	,018	,354	2,645	,012
	Quarter 4 (dummy)	,068	,018	,505	3,771	,001
	Year 2013 (dummy)	,049	,018	,362	2,729	,009
	Year 2015 (dummy)	,083	,027	,616	3,120	,003

a. Dependent Variable: Ln Sales in DDDs

Figure 10.142 – Significant variables for product PA5 in Model 8.1

Product PA5 has eight independent variables with significant coefficients, including four temporal dummy variables. Detailing flow appears with an elasticity of 0,174.

Moving to product HE1, the variables with significant coefficients were (figure 10.143):

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	24,935	1,966		12,684	,000
	Ln Sales in DDDs lagged one period	-,699	,124	-,692	-5,651	,000
	Ln Competitive global marketing expenditures flow	-,054	,026	-,159	-2,069	,046
	Ln Detailing stock (calls)	,100	,029	,498	3,476	,001
	Drug age^2	,000	,000	-2,580	-3,711	,001
	Quarter 2 (dummy)	,146	,024	,563	6,091	,000
	Quarter 3 (dummy)	,229	,039	,882	5,885	,000
	Quarter 4 (dummy)	,355	,055	1,369	6,465	,000
	Year 2013 (dummy)	,425	,064	1,637	6,631	,000
	Year 2014 (dummy)	,867	,132	3,340	6,545	,000
	Year 2015 (dummy)	1,304	,210	5,026	6,204	,000

a. Dependent Variable: Ln Sales in DDDs

Figure 10.143 – Significant variables for product HE1 in Model 8.1

Product HE1 has ten independent variables with significant coefficients, including six temporal dummy variables. Detailing stock appears with an elasticity of 0,1. It is very interesting to see the negative effect of competitive global marketing expenditures on drug sales of product HE1.

10.6.1.2. Results

It was now time to conclude whether the ten products analyzed so far evidence some type of pattern in terms of significant independent variables. Table 10.82 below summarizes the significant variables (p-values < 0,05) and correspondent coefficients.

Table 10.82 – Summary of ten products significant variables using Model 8.1

	Older	Younger	Younger	Older	Older	Younger	Younger	Younger	Older	Older
	BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE3
Constant	6,775	6,057	-3,778	32,040	28,880	17,612	47,558	11,664	24,935	12,144
Ln Sales in DDDs lagged one period	0,373	---	---	-0,582	-0,506	-0,512	---	-0,410	-0,699	---
Ln Sales in DDDs lagged two periods	---	0,485	---	---	---	---	---	---	---	0,717
Ln Detailing flow (calls)	---	---	---	---	---	---	---	0,174	---	---
Ln Journal advertising flow	---	---	---	---	0,005	---	---	---	---	---
Ln Competitive global marketing expenditures flow	---	0,094	---	---	---	0,149	---	---	-0,054	---
Ln Detailing stock	---	---	---	---	-0,262	---	0,827	---	0,100	---
Ln Other marketing expenditures stock	---	---	0,413	---	0,056	---	---	---	---	---
Ln Competitive global marketing expenditures stock	---	---	---	---	---	---	---	0,443	---	---
Ln Average drug price per DDD	---	---	---	---	-21,953	6,123	---	---	---	---
Ln Average competitors price per DDD	-1,659	---	---	-28,340	4,493	---	-229,16	---	---	---
Drug age	0,031	-0,031	0,154	-0,084	---	---	0,092	---	---	-0,052
Drug age^2	---	---	---	---	0,000	0,000	---	---	0,000	---
Ln Drug price x Ln Detailing flow	---	---	---	---	---	-0,432	---	-0,432	---	---
Ln Drug price x drug age	---	---	---	0,208	---	---	---	---	---	---
Public reimbursement	0,501	-0,107	4,762	---	---	---	---	---	---	---
Loss of exclusivity (dummy)	---	---	---	---	---	---	---	---	---	-0,221
Ipad / Tablet (% of times used in calls)	---	0,624	---	---	---	---	---	---	---	---
Laptop based materials (% of times used in calls)	---	-1,241	---	---	---	---	---	---	---	---
Printed material (% of times used in calls)	0,213	0,276	---	---	---	---	---	---	---	---
Quarter 2 (dummy)	---	0,114	---	0,135	0,090	0,161	---	---	0,146	0,238
Quarter 3 (dummy)	---	0,256	---	0,241	0,242	0,264	0,175	0,048	0,229	0,301
Quarter 4 (dummy)	0,071	0,475	---	0,364	0,357	0,370	0,176	0,068	0,355	0,538
Year 2013 (dummy)	---	0,646	---	0,325	0,308	0,426	---	0,049	0,425	0,630
Year 2014 (dummy)	---	1,252	---	---	---	0,938	---	---	.667	1,311
Year 2015 (dummy)	0,185	1,696	0,324	0,331	0,339	1,377	---	0,083	1,304	1,859

Source: own elaboration

Analyzing the table above, we realize that – excluding the dummy variables and drug age - no apparent pattern is evident, neither considering the 10 products, nor considering subgroups such as younger versus older products. Due to this finding, we decided to stop at this point, leaving products HE2, HE4, HE5, LI1, LI2, LI2, LI3, LI4 and LI5 without analysis.

10.6.2. Model 8.2 - Model 7 with stepwise regression

10.6.2.1. Procedures and outputs

As methodological and intellectual curiosity, we then decided to test full Model 7 with a stepwise regression, to see to which extent our manual removal of non-significant variables was close to an automatic variable removal by SPSS. We fully applied Model 7, excluding the already omitted variables (the ones previously removed due to multicollinearity).

We analyzed the 18 products, starting with product BL1 (figures 10.144 and 10.145).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	,997[a]	,993	,993	,118817133	,993	6927,299	1	46	,000
2	,997[b]	,994	,994	,110231388	,001	8,445	1	45	,006
3	,998[c]	,996	,995	,099373359	,001	11,371	1	44	,002
4	,998[d]	,996	,996	,094739780	,000	5,409	1	43	,025
5	,998[e]	,997	,997	,083842428	,001	12,904	1	42	,001

a. Predictors: (Constant), Ln Sales in DDDs lagged one period

b. Predictors: (Constant), Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures flow

c. Predictors: (Constant), Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures flow, Ln Average drug price per DDD

d. Predictors: (Constant), Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures flow, Ln Average drug price per DDD, Drug age

e. Predictors: (Constant), Ln Sales in DDDs lagged one period, Ln Competitive global marketing expenditures flow, Ln Average drug price per DDD, Drug age, Public reimbursement (dummy)

Figure 10.144 – Model summary – Product BL1 in Model 8.2

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	,189	,137		1,379	,175
	Ln Sales in DDDs lagged one period	,992	,012	,997	83,230	,000
2	(Constant)	-1,286	,524		-2,457	,018
	Ln Sales in DDDs lagged one period	,980	,012	,985	82,982	,000
	Ln Competitive global marketing expenditures flow	,128	,044	,034	2,906	,006
3	(Constant)	,431	,694		,620	,538
	Ln Sales in DDDs lagged one period	,871	,034	,875	25,680	,000
	Ln Competitive global marketing expenditures flow	,135	,040	,036	3,392	,001
	Ln Average drug price per DDD	-,442	,131	-,114	-3,372	,002
4	(Constant)	,987	,704		1,402	,168
	Ln Sales in DDDs lagged one period	,723	,071	,727	10,134	,000
	Ln Competitive global marketing expenditures flow	,146	,038	,039	3,805	,000
	Ln Average drug price per DDD	-,416	,125	-,107	-3,320	,002
	Drug age	,016	,007	,156	2,326	,025
5	(Constant)	3,023	,842		3,589	,001
	Ln Sales in DDDs lagged one period	,555	,079	,557	7,047	,000
	Ln Competitive global marketing expenditures flow	,068	,040	,018	1,685	,099
	Ln Average drug price per DDD	-,373	,112	-,096	-3,344	,002
	Drug age	,028	,007	,272	4,031	,000
	Public reimbursement (dummy)	,248	,069	,083	3,592	,001

a. Dependent Variable: Ln Sales in DDDs

Figure 10.145 – Coefficients – Product BL1 in Model 8.2

In this first product, five significant variables were left.

10.6.2.2. Results

We then computed the other stepwise regressions, and built table 10.83 as a summary.

Table 10.83 – Summary of significant variables using Model 8.2 (stepwise)

	Older	Younger	Younger	Older	Older	Younger	Younger	Younger	Older	Older	Older	Older	Younger	Older	Older	Older	Younger	Younger
	BL1	**BL2**	**BL3**	**PA1**	**PA2**	**PA3**	**PA4**	**PA5**	**HE1**	**HE2**	**HE3**	**HE4**	**HE5**	**LI1**	**LI2**	**LI3**	**LI4**	**LI5**
Constant	3,023	5,270	-5,457	13,981	18,683	14,352	1,949	12,706	18,481	18,599	16,853	0,234	5,132	21,749	24,406	11,063	-40,41	7,266
Ln Sales in DDDs lagged one period	0,555	0,297	---	---	-0,279	---	---	---	-0,361	-0,331	-0,463	---	---	-0,418	-0,498	---	---	0,372
Ln Sales in DDDs lagged two periods	---	0,389	---	---	---	---	---	---	---	---	0,362	0,983	---	---	-0,338	---	0,477	---
Ln Detailing flow (calls)	---	---	0,093	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ln Journal advertising flow	---	---	---	---	---	---	---	---	---	0,005	---	---	---	---	---	0,007	---	---
Ln Mailing flow	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	-0,009
Ln Competitive global marketing expenditures flow	0,068	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0,158	---	---
Ln Detailing stock	---	---	0,598	---	---	---	0,889	---	0,071	---	---	---	0,195	---	---	---	---	---
Ln Other marketing expenditures stock	---	---	0,189	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ln Average drug price per DDD	-0,373	-1,108	---	---	---	---	---	---	---	---	---	---	---	---	---	---	-72,32	---
Ln Average competitors price per DDD	---	---	---	---	-1,889	-2,507	---	---	---	-0,346	---	---	-3,726	---	0,199	---	---	---
Drug age	0,028	---	0,128	0,004	---	---	0,089	---	0,012	0,005	---	---	0,095	---	---	---	---	---
Drug age^2	---	---	---	---	---	---	---	0,0000	---	---	---	---	-0,001	---	---	---	---	---
Ln Drug price x Ln Detailing flow	---	---	---	---	---	---	---	0,144	---	---	---	---	---	---	---	---	---	---
Ln Drug price x Ln Detailing stock	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	-0,237	---	---
Public reimbursement	0,248	---	4,666	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Loss of exclusivity (dummy)	---	---	---	---	---	---	---	---	---	---	-0,278	---	---	---	---	---	---	---
Ipad / Tablet (% of times used in calls)	---	---	0,482	---	---	---	---	---	---	---	---	---	-0,352	---	---	---	---	---
Printed material (% of times used in calls)	---	---	---	---	---	---	---	---	0,116	---	---	---	---	---	---	---	---	0,298
Very useful (% of calls)	---	---	-0,572	---	---	---	---	---	---	---	---	---	0,324	---	---	---	-0,363	---
Increase / Will begin to prescribe (% of calls)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0,153	---	---
Ln Avg number of products presented during the calls	---	---	0,651	---	---	---	---	---	---	---	---	---	0,479	---	---	---	---	---
Quarter 3 (dummy)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0,046	-0,052	---
Quarter 4 (dummy)	---	---	---	---	0,046	0,040	---	---	---	---	---	---	0,128	---	---	---	---	---
Year 2013 (dummy)	---	---	---	---	---	---	---	---	---	---	---	---	---	-0,132	---	---	---	---
Year 2014 (dummy)	---	---	---	---	---	---	0,219	---	---	---	---	---	0,089	-0,057	---	---	---	---
Year 2015 (dummy)	---	---	---	---	---	---	---	---	---	---	-0,576	---	---	---	---	---	---	---
Adjusted R^2	0,997	0,977	1,000	0,517	0,539	0,705	0,957	0,192	0,825	0,596	0,883	0,978	0,993	0,291	0,496	0,516	0,927	0,614

Tabel 10.83 demonstrates the strong heterogeneity among products, in terms of their variables with significant coefficients. Again, and such as seen using Model 8.1, we did not find evident patterns, which confirms our dissatisfaction.

10.6.3. Model 8.3 – First attempt to build a final model

10.6.3.1. Procedures and outputs

Consequently, we decided to choose a theoretically robust regression model, resulting from the theory on pharmaceutical marketing. We started with model 8.1, keeping however, in each non-significant variable removal, a fixed group of variables, which have vastly been demonstrated to impact prescription behavior (measured as drug sales):

- Detailing flow
- Journal advertising flow
- Mailing (direct marketing) flow
- Detailing stock
- Average drug price per DDD
- Drug age
- Drug price x Detailing flow
- Public reimbursement (when applicable)
- Loss of exclusivity (when applicable)

Therefore, these variables were kept in the regression outputs, even if they evidenced non-significant coefficients.

Below, we present the regression output for product BL1, with the fixed applicable variables and the ones with significant coefficients (figure 10.146).

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	2,372	2,160		1,098	,280
	Ln Sales in DDDs lagged one period	,359	,095	,361	3,781	,001
	Ln Detailing flow (calls)	,023	,186	,007	,122	,903
	Ln Journal advertising flow	,006	,004	,016	1,552	,130
	Ln Mailing flow	,010	,004	,024	2,627	,013
	Ln Detailing stock (calls)	,251	,135	,078	1,858	,072
	Ln Average drug price per DDD	1,409	1,005	,363	1,402	,170
	Ln Average competitors price per DDD	-1,550	,766	-,135	-2,023	,051
	Drug age	,063	,014	,608	4,593	,000
	Ln Drug price x Ln Detailing flow	-,009	,146	-,015	-,061	,952
	Ln Drug price x drug age	-,023	,008	-,117	-2,694	,011
	Public reimbursement (dummy)	,400	,107	,134	3,736	,001
	Printed material (% of times used in calls)	,326	,160	,032	2,030	,050
	Quarter 4 (dummy)	,068	,028	,021	2,434	,020
	Year 2013 (dummy)	,102	,039	,031	2,626	,013

a. Dependent Variable: Ln Sales in DDDs

Figure 10.146 – Chosen variables for product BL1 in Model 8.3 (final model)

10.6.3.2. Results

We then proceeded with the other 17 products. Table 10.84 below evidences the fixed variables, in addition to the variables with significant coefficients. The light blue shade highlights the coefficients with sig. < 0,05, whereas the dark blue shaded ones highlight the coefficients with sig. < 0,10. The fixed variables are highlithed with a darker blue shade (first column from the left – these are the variables that were not removed, even not having, in most cases, significant coefficients).

Table 10.84 – Coefficients in Model 8.3

			Older	Younger	Younger	Older	Older	Younger	Younger	Younger	Older	Older	Older	Older	Younger	Older	Older	Older	Younger	Younger
			BL1	BL2	BL3	PA1	PA2	PA3	PA4	PA5	HE1	HE2	HE3	HE4	HE5	LI1	LI2	LI3	LI4	LI5
Constant			2,372	11,278	-9,522	31,324	31,539	18,349	24,980	11,202	23,426	24,877	27,742	22,085	4,086	25,067	23,805	11,721	-1,525	10,460
Lagged sales	Ln Sales in DDDs lagged one period		0,359			-0,551	-0,517	-0,603	-0,126		-0,608	-0,526	-0,533			-0,453	-0,536	-0,504	-0,427	
	Ln Sales in DDDs lagged two periods								-0,098											0,338
Marketing expenditures flow	**Own**	Ln Detailing flow	0,023	0,155	0,212	0,021	-0,429	0,160	0,443	0,154	0,024	-0,116	-0,010	0,137	0,120	0,004	0,011	0,927	0,036	-0,561
		Ln Journal advertising flow	0,006	0,006	0,001	-0,001	0,005	0,005	-0,014	0,001	-0,004	0,006			0,002	0,001	-0,001	0,008	-0,006	0,002
		Ln Direct marketing flow	0,010	0,001	0,009	-0,004	0,001	-0,002	-0,017	-0,004	-0,006	-0,006	0,025		0,001	-0,005	0,005	0,007	-0,002	-0,007
	Competitive	Ln Competitive marketing expenditures flow										-0,062								
Marketing expenditures stock	**Own**	Ln Detailing stock	0,251	0,033	1,250	0,027	-0,181	0,104	2,247	0,012	0,085	-0,093	0,048	1,252	0,192	-0,190	0,039	0,188	0,018	0,128
		Ln Other marketing expenditures stock																0,054		
	Competitive	Ln Competitive global marketing expenditures stock												-0,568						
Price	**Own**	Ln Average drug price per DDD	1,409	-0,719	0,887	-0,435	-31,20	9,380		4,436	1,595	0,795	-0,432	-2,739	-0,983	-0,805	-1,679	-12,62	-30,14	-7,527
	Competitors	Ln Average competitors drug price per DDD	-1,550			-27,72	3,566		-191,8					-1,521	-3,683		0,219			0,408
Drug age	Drug age		0,063	0,027	0,101	-0,087	-0,001	0,015	0,168	0,004	0,015	-0,003	-0,033	-0,029	0,102	-0,016	-0,033	0,037	0,015	0,013
	Drug age squared						-0,0002	-0,0003			-0,0002	-0,0003			-0,001			-0,0003	-0,0003	-0,001
Marketing expenditures interactions	Ln Drug price x Ln Detailing flow		-0,009	-0,117		-0,058	1,587	-0,844		-0,385		-0,116	0,008	0,099	0,113			1,745		0,959
	Ln Drug price x Ln Detailing stock													0,967						
	Ln Drug price x drug age		-0,023			0,219														
Policy change	Public reimbursement		0,400	-0,052	4,683															
	Loss of exclusivity (dummy)													-0,221						
Additional variables	Ipad / Tablet (% of times used in calls)														-0,434					
	Laptop based materials (% of times used in calls)			-1,086																
	Printed material (% of times used in calls)		0,326	0,392														-0,181	0,209	
	Very useful (% of calls)														0,321			-0,172		
	Increase / Will begin to prescribe (% of calls)																	0,205		
	Ln Avg number of products presented during the calls														0,459			0,198		
Temporal dummies	Quarter 2					0,132	0,095	0,137			0,123	0,135					0,125	0,069	0,138	0,199
	Quarter 3					0,233	0,216	0,222	0,214		0,205	0,213				0,087	0,197	0,200	0,153	0,290
	Quarter 4		0,068	0,097		0,356	0,308	0,325			0,297	0,358	0,214	0,068	0,123	0,132	0,335	0,248	0,246	0,455
	Year 2013		0,102	0,181		0,313	0,258	0,370			0,300	0,417	0,289				0,406	0,277	0,272	0,641
	Year 2014			0,217			0,339	0,808			0,701	0,894	0,382		0,077	0,232	0,818	0,656	0,538	1,108
	Year 2015					0,330	0,297	1,219			1,098	1,385				0,388	1,198	1,033	0,924	1,684
		Adjusted R^2	**0,997**	**0,986**	**1,000**	**0,757**	**0,704**	**0,841**	**0,957**	**0,136**	**0,873**	**0,791**	**0,877**	**0,984**	**0,988**	**0,148**	**0,483**	**0,667**	**0,941**	**0,779**

We then further summarized the outputs from Model 8.3, in table 10.85 below.

Table 10.85 – Summary of coefficients in Model 8.3

			Market 1 - Blood			Market 2 - Pancreas			Market 3 - Heart			Market 4 - Liver			Global		
			Avg elasticity	% signal as expected	% signal as expected and sig. <0.1	Avg elasticity	% signal as expected	% signal as expected and sig. <0.1	Avg elasticity	% signal as expected	% signal as expected and sig. <0.1	Avg elasticity	% signal as expected	% signal as expected and sig. <0.1	Avg elasticity	% signal as expected	% signal as expected and sig. <0.1
Marketing expenditures flow	**Own**	Ln Detailing flow	0,130	100,0%	0,0%	0,070	80,0%	20,0%	0,031	60,0%	0,0%	0,084	80,0%	0,0%	0,073	77,8%	5,6%
		Ln Journal advertising flow	0,004	100,0%	33,3%	-0,001	60,0%	40,0%	0,001	40,0%	20,0%	0,001	60,0%	20,0%	0,001	61,1%	27,8%
		Ln Direct marketing flow	0,007	100,0%	33,3%	-0,005	20,0%	0,0%	0,004	40,0%	20,0%	-0,001	40,0%	0,0%	0,000	44,4%	11,1%
	Competitive	Ln Competitive marketing expenditures flow	N/A	N/A	N/A	N/A	N/A	N/A	-0,062	20,0%	20,0%	N/A	N/A	N/A	-0,062	5,6%	5,6%
Marketing expenditures stock	**Own**	Ln Detailing stock	0,511	100,0%	66,7%	0,442	80,0%	20,0%	0,297	80,0%	60,0%	0,037	80,0%	20,0%	0,301	83,3%	38,9%
		Ln Other marketing expenditures stock	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0,054	20,0%	20,0%	0,054	5,6%	5,6%
	Competitive	Ln Competitive global marketing expenditures stock	N/A	N/A	N/A	N/A	N/A	N/A	-0,568	20,0%	20,0%	N/A	N/A	N/A	-0,568	5,6%	5,6%
Price	**Own**	Ln Average drug price per DDD	0,526	33,3%	0,0%	-4,455	40,0%	20,0%	-0,353	60,0%	20,0%	-10,554	100,0%	0,0%	-4,163	61,1%	11,1%
	Competitors	Ln Average competitors drug price per DDD	-1,550	0,0%	0,0%	-71,981	20,0%	20,0%	-2,602	0,0%	0,0%	0,314	40,0%	20,0%	-27,759	16,7%	11,1%
Drug age	Drug age		0,064	100,0%	100,0%	0,020	60,0%	40,0%	0,010	40,0%	0,0%	0,003	60,0%	0,0%	0,020	61,1%	27,8%
	Drug age squared		N/A	N/A	N/A	-0,0003	40,0%	40,0%	-0,0005	60,0%	60,0%	-0,0004	60,0%	60,0%	-0,0004	44,4%	44,4%
Marketing expenditures interactions	Ln Drug price x Ln Detailing flow		-0,063	0,0%	0,0%	0,075	20,0%	0,0%	0,026	60,0%	20,0%	1,352	40,0%	0,0%	0,248	33,3%	5,6%
	Ln Drug price x Ln Detailing stock		N/A	N/A	N/A	N/A	N/A	N/A	0,967	20,0%	20,0%	N/A	N/A	N/A	0,967	5,6%	5,6%
	Ln Drug price x drug age		-0,023	33,3%	33,3%	0,219	0,0%	0,0%	N/A	N/A	N/A	N/A	N/A	N/A	0,098	5,6%	5,6%
Policy change	Public reimbursement		1,677	66,7%	66,7%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1,677	66,7%	66,7%
	Loss of exclusivity (dummy)		N/A	N/A	N/A	N/A	N/A	N/A	-0,221	50,0%	50,0%	N/A	N/A	N/A	-0,221	50,0%	50,0%

10.6.3.3. Comparison of Model 8.3 against Model 7

It was now time to compare Model 7 against Model 8.3 coefficients and overall metrics (table 10.86).

Table 10.86 – Comparison of the fixed variables in Models 7 and 8.3

	Average elasticities		% signal as expected		% signal as expected and sig. <0.05	
	Model 7	Model 8.3	Model 7	Model 8.3	Model 7	Model 8.3
Ln Detailing flow	0,103	0,073	66,7%	77,8%	0,0%	5,6%
Ln Journal advertising flow	0,002	0,001	75,0%	61,1%	18,8%	22,2%
Ln Direct marketing flow	-0,001	0,0003	35,3%	44,4%	0,0%	11,1%
Ln Detailing stock	0,204	0,301	77,8%	83,3%	0,0%	33,3%
Ln Average drug price per DDD	-2,670	-4,163	64,7%	61,1%	0,0%	11,1%
Drug age	0,015	0,020	50,0%	61,1%	5,6%	22,2%
Ln Drug price x Ln Detailing flow	0,067	0,248	50,0%	33,3%	0,0%	5,6%
Public reimbursement	1,537	1,677	66,7%	66,7%	33,3%	66,7%
Loss of exclusivity (dummy)	-0,277	-0,221	100,0%	50,0%	50,0%	50,0%
			65,1%	**59,9%**	**12,0%**	**25,3%**

Source: own elaboration

Despite the fact that Model 7 apparently produced a higher percentage of coefficients with signals as expected based on the theory, Model 8.3 has a substantially higher percentage of coefficients with both the correctal signal and sig. < 0,05. Also, Model 8.3 detailing coefficients (flow and stock) have also a substantially higher percentage of products with signal as suggested by the theory. Model 8.3 seems, therefore, our best model so far.

However, model 8.3 includes temporal dummies which will not allow the correct application of the Chow (1960) test. The number of independent variables is dependent of the year dummies, where for the first 19 months of the time series (**Period 1**, before the entry into force of the detailing restriction policy) we would use the dummy Year 2013 only, and for the second 29 months (**Period 2**, after the entry into force of the detailing restriction policy) we

would use the dummies Year 2014 and Year 2015. To avoid this issue, we decided to run Model 8.3 again but **without temporal dummies**. We named this model as **Model 8.4**.

10.6.4. Model 8.4 – Final model

10.6.4.1. Procedures and outputs

As our **final model**, we performed some analyses and controls to the full model (that is, the whole dataset of 48 observations), in order to guarantee the model is adequate. This consisted of:

- **Collinearity diagnostic** – we analyzed the variable inflation factor (VIF) for each variable

  VIF = 1 / (1-R^2_j) is the R^2 of the regression when we have the variable j as dependent and as independent all the other variables. If this R^2 is high, then the VIF ratio will also be very high and will mean that the variable j will be highly correlated with the remaining variables. One can also use another ratio, called Tolerance, given by 1 - R^2_j

  In relation to VIF, the rule of thumb is to accept VIF up to 10 (meaning that we can accept R^2_j up to values of 0,9). VIFs close to 3 are considered excellent.

- **Normality of residuals** – it is important to guarantee that the residuals follow a normal distribution. At SPSS, we activated the options Save → Residuals → Unstandardized. We then explored this variable (*Analyze → Descriptives → Explore*, with the options *Histogram* and *Normality plots with tests*, and looking especially for the Shapiro-Wilk test.

  Given that normal distributions have a skewness and a Kurtosis (flatness measure) equal to zero, and as a rule of thumb, that:
  - If | Skewness | > 0,5 → we get a significant difference
  - If | Kurtosis | > 0,5 → we get a significant difference

  In other words, if in absolute value these results are not lower than 0,5, then there is not enough evidence for the residuals distribution to be considered symmetric

The hypotheses are the following:

H_0: U ~ N

H_a: U ~ N

- **Homocedasticity analysis** – a homocedastic model is one whose variation of Y does not increase with the variation (increase) of X, that is, the variance of U given X is constant (this dispersion must be constant). We saved the unstandardized residuals and calculated their square

  The hypotheses are the following:

  H_0: $V(U \mid x_1, x_2, ..., x_n) = \sigma^2$
  H_a: $V(U \mid x_1, x_2, ..., x_n) = \sigma^2 (x_1, x_2, ..., x_n)$

  The appropriate test is Breush-Pagan, where $\hat{U}^2 = B_0 + B_1X_1 + ... + B_kX_k + E$
  In order to check the homocedasticity, we performed a regression with the squared unstandardized residuals as dependent variable and the other variables as independent. Whenever the sig. output in the ANOVA was lower than 0,05, we rejected the hypothesis of homocedasticity.

- **Reset test** – we saved the unstandardized predicted values, squared them, and ran the regression again including them as an independent variable. In the cases where this variable is significant, the model appears not correctly specified. This can be called a "trick" to avoid including all squared coefficients, thus synthetizing all the coefficients of degree 2 into one variable. We also performed this for cubic coefficient.

  The hypotheses are the following:
  H_0: $\beta_i = 0$
  H_a: $\beta_i \neq 0$

Such as performed with Model 8.3, we included all variables but left a selected group of "fixed" variables (independently of their significance), and other variables that were significant.

Collinearity diagnostic

We started with Market 1 – Blood. We had to drop the dummy variable Public reimbursement too, given that it occurred during Period 2 (after the entry into force of the detailing ceiling), and would not be applicable to apply to Period 1. We did this to keep the number of variables the same in the model using 48 observations and the models using 19 and 29 observations (Periods 1 and 2, respectively). We performed the same procedures such as in previous versions of Model 8, removing, one by one, the non-significant variables and checking the R^2 change.

The next pages summarize the procedures observed regarding product BL1 (figures 10.147, 10.148, 10.149, 10.150, 10.151 and 10.152).

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-2,393	1,795		-1,333	,191		
	Ln Sales in DDDs lagged one period	,358	,111	,359	3,225	,003	,006	176,438
	Ln Detailing flow (calls)	,052	,155	,017	,335	,740	,029	35,028
	Ln Journal advertising flow	,004	,004	,010	,973	,337	,677	1,478
	Ln Mailing flow	,004	,004	,009	,838	,407	,668	1,497
	Ln Competitive global marketing expenditures flow	,116	,041	,031	2,819	,008	,579	1,726
	Ln Detailing stock (calls)	,158	,098	,049	1,619	,114	,077	13,051
	Ln Competitive global marketing expenditures stock	,333	,111	,056	3,012	,005	,204	4,914
	Ln Average drug price per DDD	,368	,702	,095	,524	,603	,002	463,311
	Drug age	,046	,010	,446	4,573	,000	,007	135,406
	Ln Drug price x Ln Detailing flow	-,117	,097	-,193	-1,206	,236	,003	365,097

a. Dependent Variable: Ln Sales in DDDs

Figure 10.147 – Regression outputs of product BL1 in Model 8.4 – iteration 1

We kept the R^2 change option activated. We can detect very high VIFs, which we find expectable given the use of a lagged variable and an interaction variable. We started by removing the interaction variable Ln Drug price x Ln Detailing flow, which provoked a substantial reduction in overall VIFs.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-1,964	1,770		-1,110	,274		
	Ln Sales in DDDs lagged one period	,387	,109	,388	3,549	,001	,006	168,177
	Ln Detailing flow (calls)	-,119	,063	-,038	-1,903	,065	,177	5,661
	Ln Journal advertising flow	,004	,004	,010	,971	,337	,677	1,478
	Ln Mailing flow	,002	,004	,006	,563	,577	,708	1,412
	Ln Competitive global marketing expenditures flow	,135	,038	,036	3,534	,001	,679	1,472
	Ln Detailing stock (calls)	,149	,098	,046	1,526	,135	,077	12,980
	Ln Competitive global marketing expenditures stock	,359	,109	,060	3,294	,002	,212	4,724
	Ln Average drug price per DDD	-,453	,169	-,117	-2,681	,011	,038	26,615
	Drug age	,046	,010	,441	4,495	,000	,007	135,123

a. Dependent Variable: Ln Sales in DDDs

Figure 10.148 – Regression outputs of product BL1 in Model 8.4 – iteration 2

We then removed the lagged variable (Ln Sales in DDDs lagged one period), which allowed a further reduction in VIFs.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-2,507	2,009		-1,248	,220		
	Ln Detailing flow (calls)	-,205	,066	-,066	-3,112	,003	,207	4,820
	Ln Journal advertising flow	,005	,004	,014	1,184	,244	,684	1,462
	Ln Mailing flow	,001	,005	,003	,292	,772	,711	1,406
	Ln Competitive global marketing expenditures flow	,136	,043	,036	3,122	,003	,680	1,472
	Ln Detailing stock (calls)	,165	,111	,051	1,484	,146	,077	12,953
	Ln Competitive global marketing expenditures stock	,631	,088	,106	7,160	,000	,420	2,384
	Ln Average drug price per DDD	-,642	,183	-,165	-3,510	,001	,042	23,987
	Drug age	,080	,004	,773	22,635	,000	,079	12,607
2	Ln Avg number of products presented during the calls	-,229	,223	-,021	-1,026	,313	,183	5,458

a. Dependent Variable: Ln Sales in DDDs

Figure 10.149 – Regression outputs of product BL1 in Model 8.4 – iteration 3

This decision had no significant impact on R^2, as seen below.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	,998[a]	,996	,996	,095377989	,996	1347,852	8	39	,000
2	,999[b]	,998	,997	,085507108	,002	1,866	11	28	,089

a. Predictors: (Constant), Drug age, Ln Mailing flow, Ln Competitive global marketing expenditures flow, Ln Journal advertising flow, Ln Competitive global marketing expenditures stock, Ln Detailing flow (calls), Ln Detailing stock (calls), Ln Average drug price per DDD

b. Predictors: (Constant), Drug age, Ln Mailing flow, Ln Competitive global marketing expenditures flow, Ln Journal advertising flow, Ln Competitive global marketing expenditures stock, Ln Detailing flow (calls), Ln Detailing stock (calls), Ln Average drug price per DDD, Very useful (% of calls), Laptop based materials (% of times used in calls), Printed material (% of times used in calls), Ln Other marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Ln Drug price x drug age, Ln Average competitors price per DDD, Ln Sales in DDDs lagged two periods, Ln Sales in DDDs lagged one period

Figure 10.150 – R^2 change of product BL1 in Model 8.4 (iteration 3)

The next decision was to remove the variable Ln Average drug price per DDD, which had the highest VIF. The VIFs suffered a further reduction.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-8,178	1,352		-6,047	,000		
	Ln Detailing flow (calls)	-,091	,065	-,029	-1,405	,168	,274	3,656
	Ln Journal advertising flow	,001	,005	,004	,291	,773	,728	1,373
	Ln Mailing flow	,003	,006	,006	,496	,623	,716	1,397
	Ln Competitive global marketing expenditures flow	,131	,049	,035	2,665	,011	,680	1,470
	Ln Detailing stock (calls)	,350	,111	,109	3,145	,003	,099	10,066
	Ln Competitive global marketing expenditures stock	,785	,087	,132	9,062	,000	,557	1,794
	Drug age	,086	,003	,831	24,585	,000	,104	9,631

a. Dependent Variable: Ln Sales in DDDs

Figure 10.151 – Regression outputs of product BL1 in Model 8.4 – iteration 4

This provoked, however, a significant reduction in the R^2.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	,998[a]	,995	,994	,108037850	,995	1199,173	7	40	,000
2	,999[b]	,998	,997	,085507108	,003	2,988	12	28	,008

a. Predictors: (Constant), Drug age, Ln Mailing flow, Ln Competitive global marketing expenditures flow, Ln Journal advertising flow, Ln Competitive global marketing expenditures stock, Ln Detailing flow (calls), Ln Detailing stock (calls)

b. Predictors: (Constant), Drug age, Ln Mailing flow, Ln Competitive global marketing expenditures flow, Ln Journal advertising flow, Ln Competitive global marketing expenditures stock, Ln Detailing flow (calls), Ln Detailing stock (calls), Very useful (% of calls), Laptop based materials (% of times used in calls), Printed material (% of times used in calls), Ln Other marketing expenditures stock, Increase / Will begin to prescribe (% of calls), Ln Drug price x drug age, Ipad / Tablet (% of times used in calls), Ln Avg number of products presented during the calls, Ln Average competitors price per DDD, Ln Sales in DDDs lagged two periods, Ln Average drug price per DDD, Ln Sales in DDDs lagged one period

Figure 10.152 – R^2 change of product BL1 in Model 8.4 (iteration 3)

Therefore, we reintroduced this last removed variable again in the regression. We accept relatively high VIFs in the cases where the removal of certain variables provoke significant reductions in the R^2. By other words, we accept having a lower precision of the parameter estimates (confidence interval amplitude).

We then faced a difficult situation. By the one hand, there are sources of multicollinearity, evident in three of the variables, which would suggest us to remove at least Detailing stock (created having at its base the variable Detailing flow). By the other hand, if we remove these core variables from our model our ability to interpret the results in light of the theory would be substantially limited. Therefore, taking into account the pros and cons, we decided to keep those fixed variables in our model, assuming, in conscience, it is not the most correct or scientific one. This was the same assumption we observed regarding the other products analyzed. As a general rule, we tried to keep, in the regressions, the fixed set of variables discussed before, with the exception of the lagged sales terms and the interaction variable Ln Drug price x Ln Detailing flow.

Normality of residuals

We then moved to the analysis of the normality of the residuals, still regarding product BL1 (figures 10.153, 10.154, 10.155 and 10.156).

Descriptives

			Statistic	Std. Error
Unstand. residuals BL1	Mean		,0000000	,00952602
	95% Confidence Interval for Mean	Lower Bound	-,0191639	
		Upper Bound	,0191639	
	5% Trimmed Mean		-,0004353	
	Median		,0032834	
	Variance		,004	
	Std. Deviation		,06599823	
	Minimum		-,14112	
	Maximum		,15770	
	Range		,29882	
	Interquartile Range		,08822	
	Skewness		-,027	,343
	Kurtosis		-,043	,674

Figure 10.153 – Skewness and Skewness of product BL1 in Model 8.4

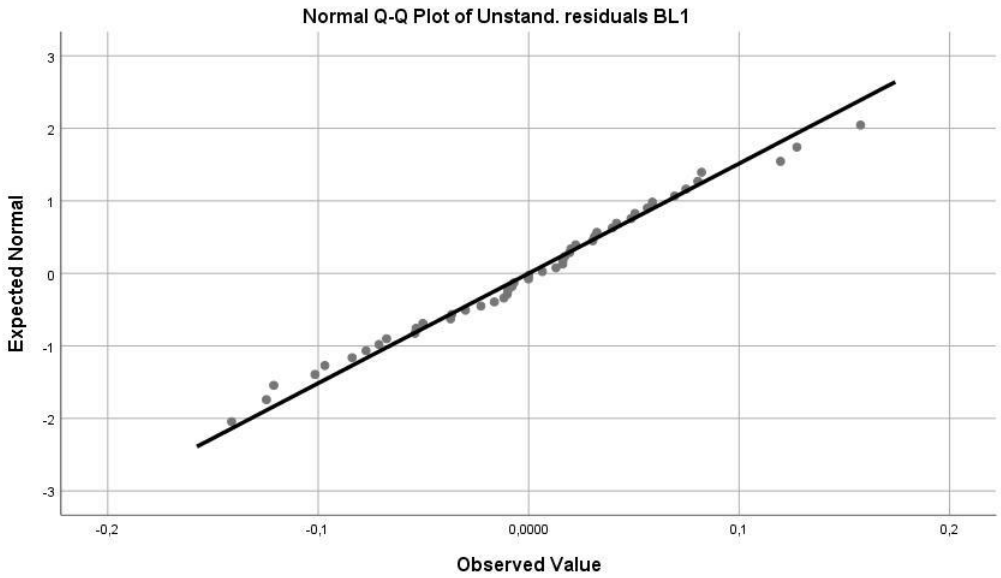
Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Unstand. residuals BL1	,075	48	,200*	,989	48	,931

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Figure 10.154 – Test of normality of residuals of product BL1 in Model 8.4



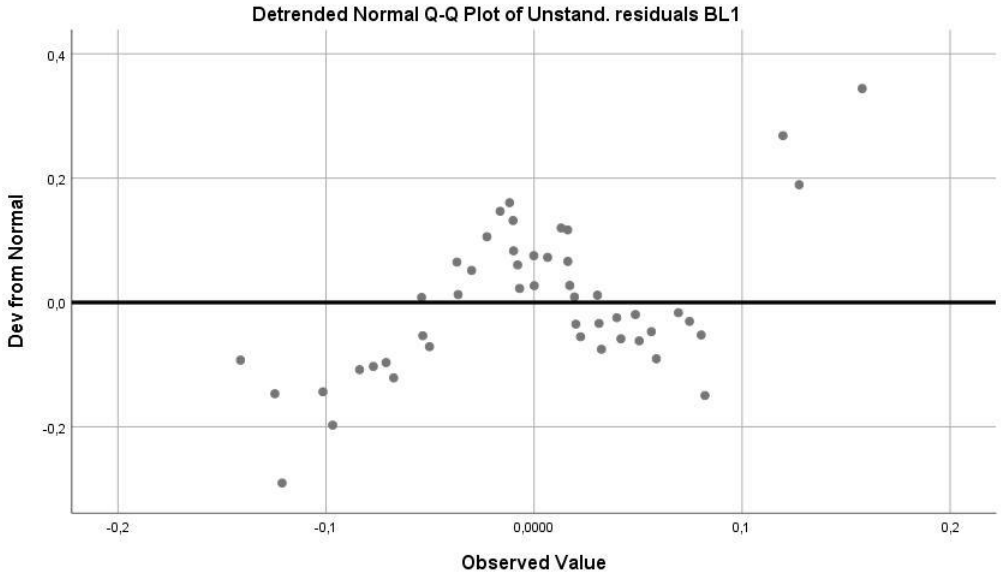


Figure 10.155 – Plots of residuals of product BL1 in Model 8.4

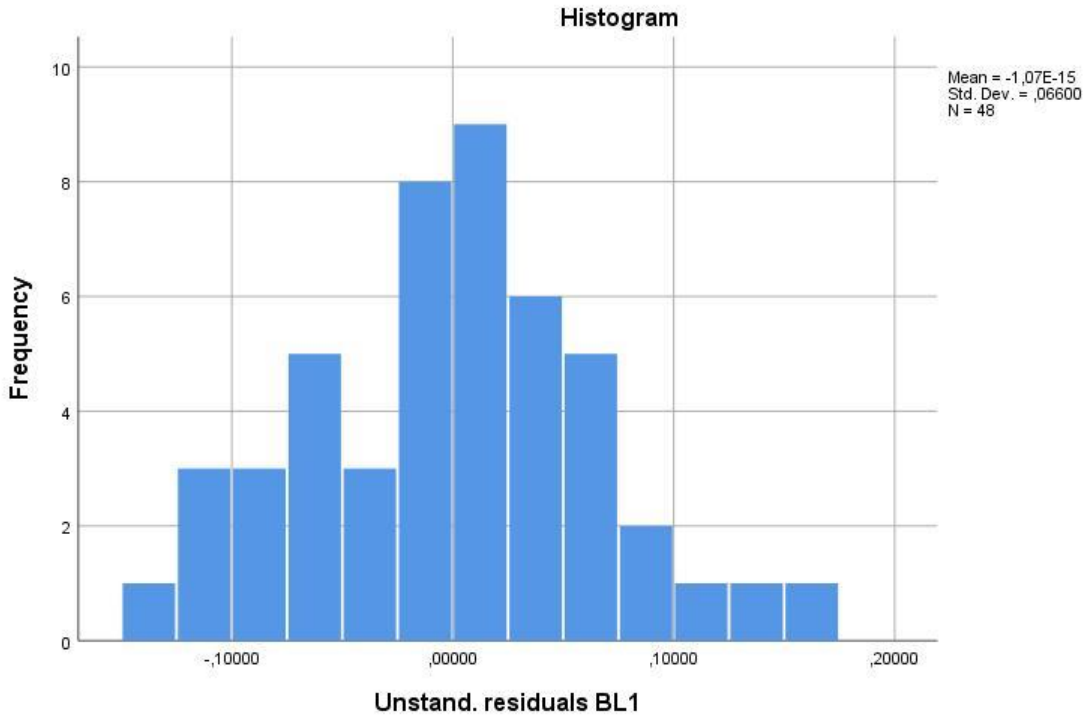


Figure 10.156 – Histogram of unstandardized residuals of product BL1 in Model 8.4

Both kurtosis and skweness are lower than 0,5 (in absolute terms), and we did not reject the hypothesis that the residuals follow a normal distribution, based on the outputs of the Shapiro-Wilk test (sig. = 0,931), so we assume the normality of the residuals.

Homocedasticity analysis

We then moved to the analysis of homodedasticity (figure 10.157). Using the squared residuals as the dependent variable, we looked at the ANOVA output.

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	,000	8	,000	,407	,910[b]
	Residual	,001	39	,000		
	Total	,002	47			

a. Dependent Variable: Squared unstand. res. BL1

b. Predictors: (Constant), Drug age, Ln Mailing flow, Ln Competitive global marketing expenditures flow, Ln Journal advertising flow, Ln Competitive global marketing expenditures stock, Ln Detailing flow (calls), Ln Detailing stock (calls), Ln Average drug price per DDD

Figure 10.157 – ANOVA output in the scope of homocesdasticity analysis of product BL1 in Model 8.4

Given that the sig. is higher than 0,05, we do not reject the null hypothesis, that is, the R^2 of this regression is not significantly different from zero.

Reset test

Finally we performed the reset test. We started with a quadratic term (figure 10.158).

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	1,075	3,704		,290	,773
	Ln Detailing flow (calls)	-,109	,106	-,035	-1,034	,308
	Ln Journal advertising flow	,004	,004	,010	,844	,404
	Ln Mailing flow	,001	,005	,002	,198	,844
	Ln Competitive global marketing expenditures flow	,076	,068	,020	1,127	,267
	Ln Detailing stock (calls)	,180	,112	,056	1,611	,115
	Ln Competitive global marketing expenditures stock	,320	,285	,054	1,121	,270
	Ln Average drug price per DDD	-,432	,258	-,111	-1,671	,103
	Drug age	,047	,029	,455	1,638	,110
	Squared unstand. predicted values for BL2	,016	,014	,377	1,149	,258

a. Dependent Variable: Ln Sales in DDDs

Figure 10.158 – Quadratic RESET test for product BL1 in Model 8.4

And also performed the test using the cubed term (figure 10.159).

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-,022	2,905		-,008	,994
	Ln Detailing flow (calls)	-,144	,083	-,046	-1,730	,092
	Ln Journal advertising flow	,005	,004	,013	1,101	,278
	Ln Mailing flow	,001	,005	,003	,229	,820
	Ln Competitive global marketing expenditures flow	,101	,052	,027	1,918	,063
	Ln Detailing stock (calls)	,212	,118	,066	1,802	,079
	Ln Competitive global marketing expenditures stock	,430	,192	,072	2,233	,032
	Ln Average drug price per DDD	-,545	,200	-,140	-2,728	,010
	Drug age	,061	,016	,592	3,770	,001
	Cubed unstand. predicted values for BL2	,000	,000	,200	1,179	,246

a. Dependent Variable: Ln Sales in DDDs

Figure 10.159 – Cubic RESET test for product BL1 in Model 8.4

In both cases, the variables coefficients are non-significant, and therefore we can conclude the model is well specified in relation to eventual quadratic and cubed terms.

We then replicated the analysis for the rests of the products. Some products were not analyzed due to an insufficient number of observations (or inexistence of observations at all) before the entry into force of the detailing ceiling:

- Product BL3 - was launched 12 months after the entry into force of the detailing ceiling
- Product PA4 - was launched four months before the entry into force of the detailing ceiling
- Product HE5 - was launched six months before the entry into force of the detailing ceiling

Also, in some of the products we were not able to use some independent variables, so that we could have the same number of variables in Period 1 and Period, a condition to apply the Chow (1960) test:

- Products HE1 and HE4 - the variables Ln Journal advertising flow and Ln Direct marketing flow were not included due to the fact that in Period 1 there were no investments

- Product HE3 – the variable Ln Journal advertising flow was not included due to the fact that in Period 1 there were no investments

- Products LI2, LI3 and LI4 - the variable Ln Direct marketing flow was not included due to the fact that in Period 1 there were no investments

Table 10.87 below summarizes the coefficients obtained in all regressions, using the whole dataset for all products, using SPSS. An updated table with products LI4 and LI5 coefficients obtained with the statistical software Eviews will be shown later (heterocedasticity).

Table 10.87 – Summary of coefficients in Model 8.4

			BL1	BL2	PA1	PA2	PA3	PA5	HE1	HE2	HE3	HE4	LI1	LI2	LI3	LI4	LI5
Constant			-2,507	6,454	12,529	18,402	15,835	6,294	19,188	14,336	22,192	-0,817	16,977	26,458	12,752	-0,508	8,599
Lagged sales	Ln Sales in DDDs lagged one period					-0,360	-0,402		-0,377			0,518		-0,564			
	Ln Sales in DDDs lagged two periods			0,585								0,487		-0,350			
Marketing expenditures flow	**Own**	Ln Detailing flow	-0,205	0,063	0,032	0,002	-0,027	0,058	-0,001	0,024	-0,011	0,025	-0,023	0,010	0,019	0,092	-0,028
		Ln Journal advertising flow	0,005	0,005	0,000	0,003	0,002	0,001		0,006			0,001	-0,001	0,008	-0,004	-0,001
		Ln Direct marketing flow	0,001	0,002	-0,004	-0,001	-0,004	-0,006		-0,002	0,014		-0,005				-0,013
	Competitive	Ln Competitive marketing expenditures flow	0,136														0,121
Marketing expenditures stock	**Own**	Ln Detailing stock	0,165	-0,011	0,195	0,076	0,214	-0,049	0,099	-0,082	0,053	0,018	-0,112	0,031	0,093	-0,012	0,150
	Competitive	Ln Competitive global marketing expenditures stock	0,631					0,406									
Price	**Own**	Ln Average drug price per DDD	-0,642	-1,471	-0,897	-0,637	1,475	1,675	1,048	-0,279	-1,769	-0,268	0,672	-1,903	-1,826	-19,76	
	Competitors	Ln Average competitors drug price per DDD								-0,348	5,078			0,232			0,282
Drug age	Drug age		0,080	0,002	0,003	0,005	0,041	0,009	0,015		-0,030	0,002	-0,002	-0,001	-0,003	0,015	0,012
	Drug age squared						-0,0003										
Additional variables	Ipad / Tablet (% of times used in calls)										0,198						
	Printed material (% of times used in calls)					0,145										0,243	0,411
		Adjusted R^2	**0,995**	**0,975**	**0,528**	**0,527**	**0,774**	**0,270**	**0,802**	**0,483**	**0,842**	**0,975**	**-0,064**	**0,492**	**0,357**	**0,923**	**0,611**

Coefficient cells highlighted in light blue have sig. < 0,05, and cells with darker blue have sig. < 0,10.

Table 10.88 below summarizes the conclusions on the good specification of the models using SPSS. This table will be later updated after running products LI4 and LI5 regressions with Eviews.

Table 10.88 – Summary of the good specification analysis – Model 8.4 before the use of Eviews in products LI4 and LI5

		Blood		Pancreas				Heart				Liver				
		BL1	BL2	PA1	PA2	PA3	PA5	HE1	HE2	HE3	HE4	LI1	LI2	LI3	LI4	LI5
Collinearity diagnostics	All VIFs < 10?	No	No	Yes	No	No	No	No	Yes	No	No	Yes	No	Yes	No	No
Normality of residuals	| Skewness | < 0.5?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
	| Kurtosis | < 0.5?	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	No
	Shapiro-Wilk Sig. > 0.05?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Homocedasticity diagnostics	ANOVA Sig. > 0.05?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Reset test	Quadratic coeff. Sig. > 0.05?	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No
	Cubic coeff. Sig. > 0.05?	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No

Source: own elaboration

In some of the regressions, we had to accept high or very high VIFs. This was especially evident in products:

- PA3 - when we removed, independently, the variables Drug age and Drug age squared, the R^2 Sig. F change produced a value lower than 5%, and therefore we decided to keep both variables in the final model, despite their very high VIFs

- HE1 - when we removed the variable Drug age, the R^2 Sig. F change produced a value lower than 5%, and therefore we decided to keep tje variable in the final model, despite its high VIF

- HE2 - when we removed the variable Drug age, the R^2 Sig. F change produced a value lower than 5%. However, since the variable was automatically excluded by SPSS due to its high VIF when using Period 1 regression, we decided to remove the variable

(and be able to proceed to the Chow (1960) test, having the same number of variables in the three models - Global, Period 1 and Period 2)

- HE4 - when we removed, independently, the variables Ln Sales in DDDs lagged one and two periods, the R^2 Sig. F change produced a value lower than 5%, and therefore we decided to keep both variables in the final model, despite their very high VIFs

- LI4 - when we removed, independently, the variable Drug age, the R^2 Sig. F change produced a value lower than 5%, and therefore we decided to keep it in the final model, despite its high VIF

- LI5 - when we removed, independently, the variables Drug age and Ln Average competitors price per DDD, the R^2 Sig. F change produced a value lower than 5%, and therefore we decided to keep both variables in the final model, despite their high VIFs

Only one product, HE4, evidenced a Sig. < 0,05 in the Shapiro-Wilk test (0,033, to be precise), which does not dramatically impact the quality of the model.

We detected a problem of heterocedasticity in the case of products LI4 and LI5. To solve this issue, we ran the regressions for these two products using the statistical software Eviews version 10+ University Edition.

We started by preparing two Excel files, one with product LI4 time series, and other with product LI5 time series. We then imported each of these files to eviews, using one at the time. We followed exactly the same procedures as the ones observed in SPSS with the other products, with the natural adaptations given that SPSS and eviews menus and options differ substantially.

Our list of variables is shown below, for product 4 (figure 10.160):

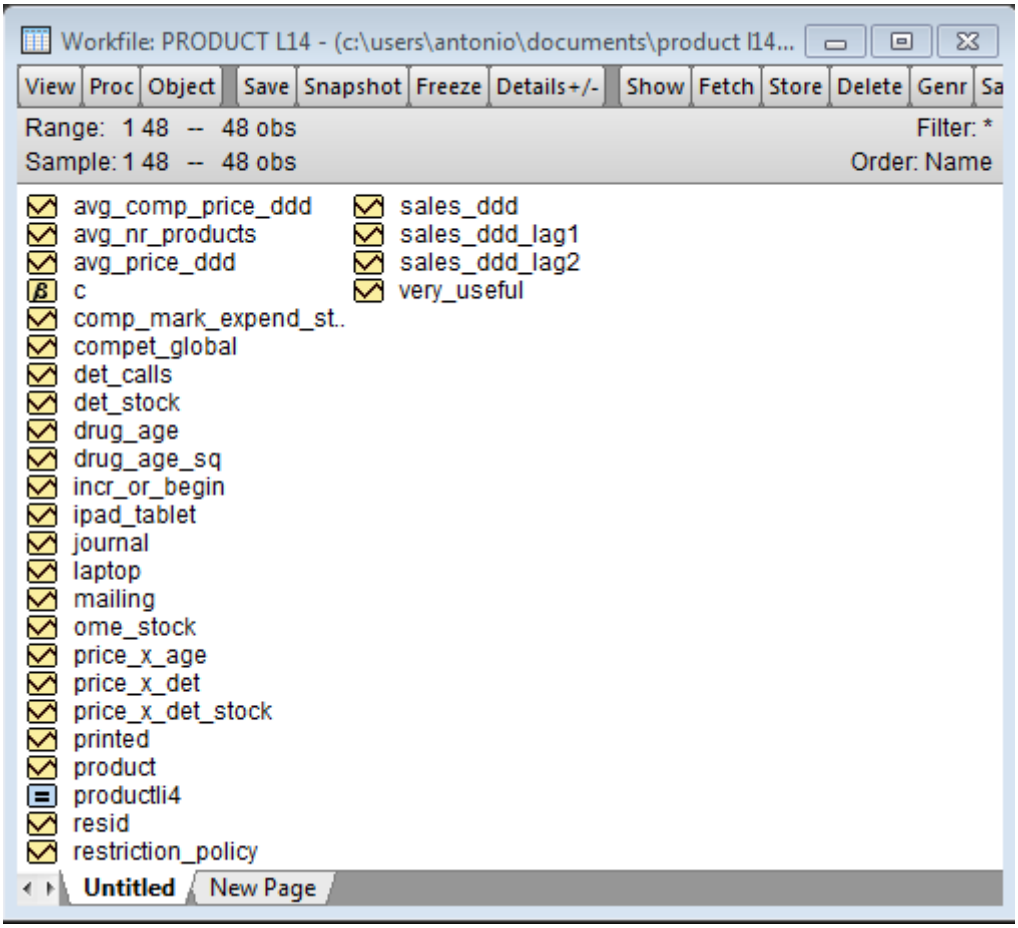
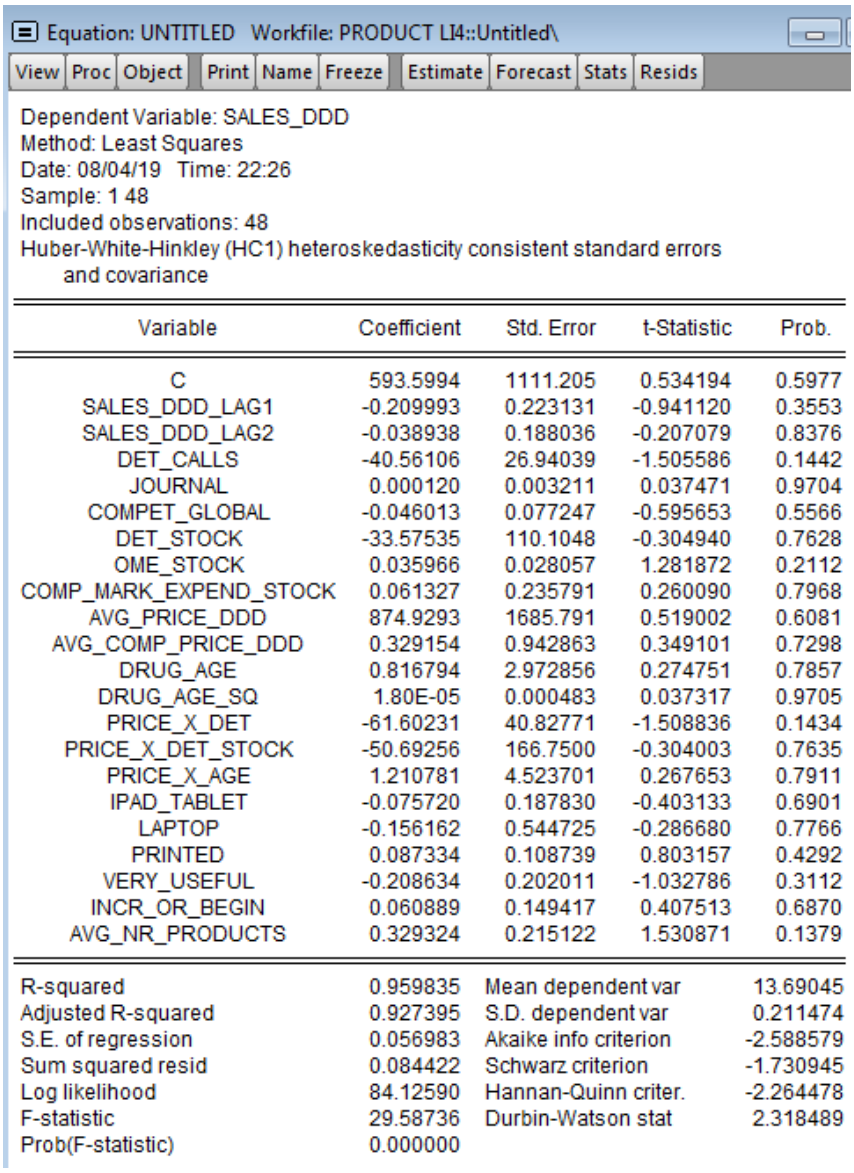


Figure 10.160 – List of variables used in Eviews for products LI4

In this equation, we removed the variable Ln Direct Marketing flow, given that it does not have observations in period 1. We used the method Huber-White for covariance method.

We ran the regressions for product LI4 first, taking into consideration the VIF and R^2 change. The screenshots below evidence the main procedures we observed (figure 10.161).



Equation: UNTITLED Workfile: PRODUCT LI4::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/04/19 Time: 22:26
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	593.5994	1111.205	0.534194	0.5977
SALES_DDD_LAG1	-0.209993	0.223131	-0.941120	0.3553
SALES_DDD_LAG2	-0.038938	0.188036	-0.207079	0.8376
DET_CALLS	-40.56106	26.94039	-1.505586	0.1442
JOURNAL	0.000120	0.003211	0.037471	0.9704
COMPET_GLOBAL	-0.046013	0.077247	-0.595653	0.5566
DET_STOCK	-33.57535	110.1048	-0.304940	0.7628
OME_STOCK	0.035966	0.028057	1.281872	0.2112
COMP_MARK_EXPEND_STOCK	0.061327	0.235791	0.260090	0.7968
AVG_PRICE_DDD	874.9293	1685.791	0.519002	0.6081
AVG_COMP_PRICE_DDD	0.329154	0.942863	0.349101	0.7298
DRUG_AGE	0.816794	2.972856	0.274751	0.7857
DRUG_AGE_SQ	1.80E-05	0.000483	0.037317	0.9705
PRICE_X_DET	-61.60231	40.82771	-1.508836	0.1434
PRICE_X_DET_STOCK	-50.69256	166.7500	-0.304003	0.7635
PRICE_X_AGE	1.210781	4.523701	0.267653	0.7911
IPAD_TABLET	-0.075720	0.187830	-0.403133	0.6901
LAPTOP	-0.156162	0.544725	-0.286680	0.7766
PRINTED	0.087334	0.108739	0.803157	0.4292
VERY_USEFUL	-0.208634	0.202011	-1.032786	0.3112
INCR_OR_BEGIN	0.060889	0.149417	0.407513	0.6870
AVG_NR_PRODUCTS	0.329324	0.215122	1.530871	0.1379

R-squared	0.959835	Mean dependent var	13.69045
Adjusted R-squared	0.927395	S.D. dependent var	0.211474
S.E. of regression	0.056983	Akaike info criterion	-2.588579
Sum squared resid	0.084422	Schwarz criterion	-1.730945
Log likelihood	84.12590	Hannan-Quinn criter.	-2.264478
F-statistic	29.58736	Durbin-Watson stat	2.318489
Prob(F-statistic)	0.000000		

Figure 10.161 – Coefficients obtained in Eviews – first iteration - product LI4

These outputs represent our first iteration. We then started to remove variables, one by one. The main candidate would be Drug age squared (Sig. = 0,9705). The next candidate to be removed was Ln Journal Advertising flow (Probability = 0,9638), but given that this is one of the fixed variables, we did not remove it. We then continued the analysis by removing the non-significant variables, until we reached a final equation. The sequence of variables removed was the following:

- Drug age squared
- Ln Sales in DDDs lagged two periods
- Ln Average drug price per DDD x Drug age
- % of calls where the reps used laptop based materials

- % of calls where doctors declared they would increase or start prescribing the product
- Ln Competitive global marketing expenditures stock
- Ln Average competitors price per DDD
- % of calls the reps used Ipad / Tablet
- Ln Competitive global marketing expenditures flow
- % of calls where the doctor received printed material
- Ln Sales in DDDs lagged one period
- Ln Average drug price per DDD x Ln Detailing stock
- % of calls where doctors considered the information received as very useful

Figure 10.162 shows our model (with the significant variables and the ones that are fixed, even non-significant):

Equation: UNTITLED Workfile: EVIEWS - PRODUCT LI4::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/04/19 Time: 23:20
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	453.6298	81.43070	5.570747	0.0000
DET_CALLS	-59.22403	9.557512	-6.196595	0.0000
JOURNAL	0.000668	0.002729	0.244813	0.8079
DET_STOCK	-0.091537	0.107166	-0.854167	0.3982
OME_STOCK	0.040002	0.019689	2.031634	0.0490
AVG_PRICE_DDD	668.2882	122.6586	5.448358	0.0000
DRUG_AGE	0.012759	0.003098	4.118255	0.0002
PRICE_X_DET	-89.91700	14.50280	-6.199976	0.0000
AVG_NR_PRODUCTS	0.333012	0.119385	2.789399	0.0081

R-squared	0.947193	Mean dependent var	13.69045
Adjusted R-squared	0.936361	S.D. dependent var	0.211474
S.E. of regression	0.053348	Akaike info criterion	-2.856593
Sum squared resid	0.110995	Schwarz criterion	-2.505743
Log likelihood	77.55824	Hannan-Quinn criter.	-2.724006
F-statistic	87.44255	Durbin-Watson stat	2.420997
Prob(F-statistic)	0.000000	Wald F-statistic	128.6271
Prob(Wald F-statistic)	0.000000		

Figure 10.162 – Coefficients obtained in Eviews – after manual removal of variables - product LI4

We then had to look at the VIFs of these variables, to decide whether we needed to proceed with the removal of additional variables. We went to View → Coefficient Diagnostics → Variance Inflation Factors and obtained an error message (figure 10.163):

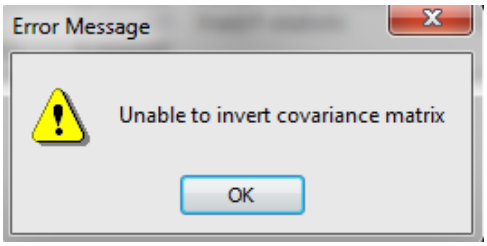


Figure 10.163 – Error message when calculating the product LI4 VIFs with Eviews

We tested the model with Ordinary Covariance Method (instead of Huber-White) and there was no invertibility problems. By other words, with non-robust estimation (Ordinary) we do not have invertibility problems, although obtaining a matrix of covariances with a determinant very close to zero, ie, it does not reach the threshould to be considered approximately singular. In the case of robust estimation (Huber-White) we obtained an indication of non-invertibility of the covariance matrix, although having a higher determinant than the previous one (with non-robust estimation). Unable to understand the source of this error, we believe this may potentially represent a bug in Eviews.

Despite this limitation, we suspect from multicollinearity in some of the significant variables, especially in Ln Drug price x Ln Detailing flow, due to abnormal coefficients of the separate variables (Ln Detailing flow, and Ln Average Drug price per DDD). To test our suspicion, we ran a non-robust (Ordinary) regression with the same independent variables and obtained the respective VIFs, here show below (figure 10.164).

Equation: EQ01_FINAL_LI4 Workfile: EVIEWS - PRODUCT LI4...

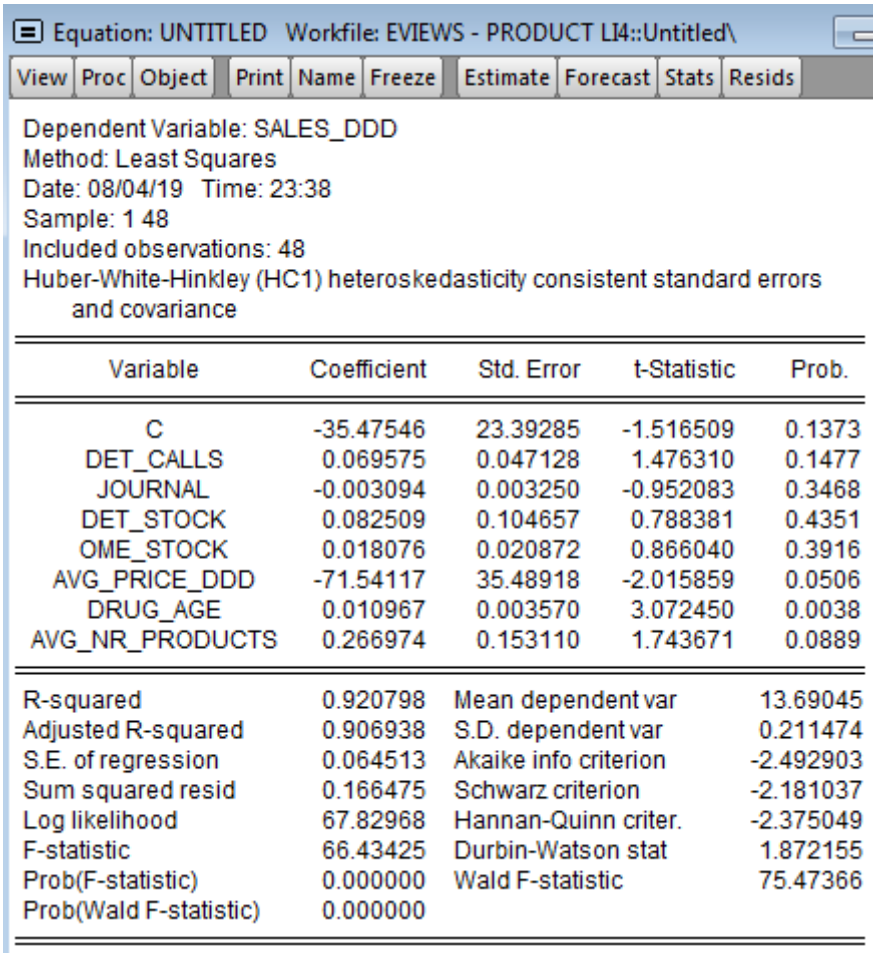
View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Variance Inflation Factors
Date: 08/12/19 Time: 12:15
Sample: 1 48
Included observations: 48

Variable	Coefficient Variance	Uncentered VIF	Centered VIF
C	12626.70	2.13E+08	NA
DET_CALLS	180.3540	1.87E+08	358245.0
JOURNAL	7.44E-06	1.656625	1.312481
DET_STOCK	0.009721	12541.44	11.59747
OME_STOCK	0.000328	539.9557	2.591337
AVG_PRICE_DDD	28912.24	2.12E+08	758.1077
DRUG_AGE	1.22E-05	230.5584	39.43086
PRICE_X_DET	414.7541	1.87E+08	337558.9
AVG_NR_PRODUCTS	0.020018	160.5664	1.462722

Figure 10.164 – VIFs for product LI4 with Eviews (Ordinary)

Indeed the interaction variable Ln Drug price x Ln Detailing flow evidences an extremely high VIF and needs to be removed from our equation. We now got back to the Huber-White method. With the removal of the interaction, the overall model became more intuitive to interpret, with variable signals much more in line with the theory on pharmaceutical marketing and detailing (figure 10.165):



Equation: UNTITLED Workfile: EVIEWS - PRODUCT LI4::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/04/19 Time: 23:38
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-35.47546	23.39285	-1.516509	0.1373
DET_CALLS	0.069575	0.047128	1.476310	0.1477
JOURNAL	-0.003094	0.003250	-0.952083	0.3468
DET_STOCK	0.082509	0.104657	0.788381	0.4351
OME_STOCK	0.018076	0.020872	0.866040	0.3916
AVG_PRICE_DDD	-71.54117	35.48918	-2.015859	0.0506
DRUG_AGE	0.010967	0.003570	3.072450	0.0038
AVG_NR_PRODUCTS	0.266974	0.153110	1.743671	0.0889

R-squared	0.920798	Mean dependent var	13.69045
Adjusted R-squared	0.906938	S.D. dependent var	0.211474
S.E. of regression	0.064513	Akaike info criterion	-2.492903
Sum squared resid	0.166475	Schwarz criterion	-2.181037
Log likelihood	67.82968	Hannan-Quinn criter.	-2.375049
F-statistic	66.43425	Durbin-Watson stat	1.872155
Prob(F-statistic)	0.000000	Wald F-statistic	75.47366
Prob(Wald F-statistic)	0.000000		

Figure 10.165 – Coefficients obtained in Eviews – removal of interaction variable - product LI4

Despite the fact that the interaction variable was signicant, its maintenance would provoke illogical coefficient signals in the individual variables it is made of (Ln Detailing flow, and Ln Average drug price per DDD), and resulting in abnormal coefficient magnitudes. We will later confirm this variable was not relevant.

Now that we have non-significant variables again, we continued the removal of the variables:

- Ln Other marketing expenditures stock
- Ln Avg number of products presented during the calls

The final iteration of the model produced the output below (figure 10.166):

Equation: UNTITLED Workfile: EVIEWS - PRODUCT LI4::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/04/19 Time: 23:45
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-38.51882	23.91930	-1.610365	0.1148
DET_CALLS	0.054337	0.042712	1.272148	0.2103
JOURNAL	-0.002821	0.003037	-0.928992	0.3582
DET_STOCK	-0.009977	0.094655	-0.105408	0.9166
AVG_PRICE_DDD	-78.23686	36.53956	-2.141155	0.0381
DRUG_AGE	0.008142	0.003468	2.347736	0.0237

R-squared	0.914685	Mean dependent var	13.69045
Adjusted R-squared	0.904529	S.D. dependent var	0.211474
S.E. of regression	0.065342	Akaike info criterion	-2.501889
Sum squared resid	0.179323	Schwarz criterion	-2.267989
Log likelihood	66.04534	Hannan-Quinn criter.	-2.413498
F-statistic	90.05917	Durbin-Watson stat	1.788245
Prob(F-statistic)	0.000000	Wald F-statistic	101.8587
Prob(Wald F-statistic)	0.000000		

Figure 10.166 – Coefficients obtained in Eviews – final interaction – product LI4

We then tried to obtain the VIFs again, and this time it did not produce an error, which increases our suspicion of some bug in Eviews when dealing with likely very strong multicollinearity.

The output below shows the VIFs (figure 10.167):

Equation: UNTITLED Workfile: EVIEWS - PRODUCT LI4::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

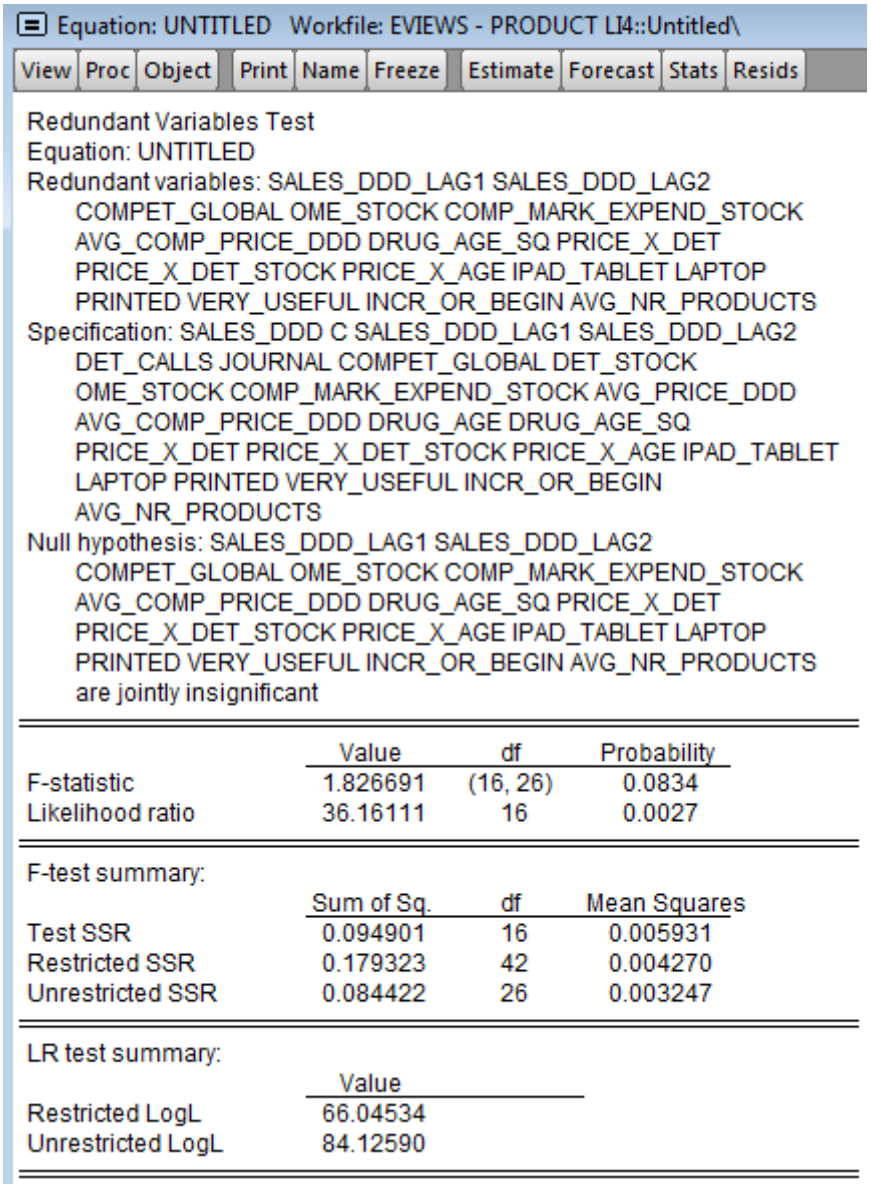
Variance Inflation Factors
Date: 08/04/19 Time: 23:48
Sample: 1 48
Included observations: 48

Variable	Coefficient Variance	Uncentered VIF	Centered VIF
C	572.1331	8935620.	NA
DET_CALLS	0.001824	1773.441	2.057744
JOURNAL	9.22E-06	2.050048	1.286036
DET_STOCK	0.008960	10807.19	8.299428
AVG_PRICE_DDD	1335.140	9081772.	22.40694
DRUG_AGE	1.20E-05	197.3718	30.58011

Figure 10.167 – VIFs for product LI4 with Eviews (Huber-White)

Despite the relatively high VIFs in two of the variables, we opted to keep them in the model.

We had to guarantee, however, that all the removed variables were redundant for R^2 change purposes. To do this, we used the option Redundant variables test, in View → Coefficient diagnosis. We compared the initial equation against the initial equation without all the discarded variables. The output we obtained is shown below (figure 10.168):



Equation: UNTITLED Workfile: EVIEWS - PRODUCT LI4::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Redundant Variables Test
Equation: UNTITLED
Redundant variables: SALES_DDD_LAG1 SALES_DDD_LAG2 COMPET_GLOBAL OME_STOCK COMP_MARK_EXPEND_STOCK AVG_COMP_PRICE_DDD DRUG_AGE_SQ PRICE_X_DET PRICE_X_DET_STOCK PRICE_X_AGE IPAD_TABLET LAPTOP PRINTED VERY_USEFUL INCR_OR_BEGIN AVG_NR_PRODUCTS
Specification: SALES_DDD C SALES_DDD_LAG1 SALES_DDD_LAG2 DET_CALLS JOURNAL COMPET_GLOBAL DET_STOCK OME_STOCK COMP_MARK_EXPEND_STOCK AVG_PRICE_DDD AVG_COMP_PRICE_DDD DRUG_AGE DRUG_AGE_SQ PRICE_X_DET PRICE_X_DET_STOCK PRICE_X_AGE IPAD_TABLET LAPTOP PRINTED VERY_USEFUL INCR_OR_BEGIN AVG_NR_PRODUCTS
Null hypothesis: SALES_DDD_LAG1 SALES_DDD_LAG2 COMPET_GLOBAL OME_STOCK COMP_MARK_EXPEND_STOCK AVG_COMP_PRICE_DDD DRUG_AGE_SQ PRICE_X_DET PRICE_X_DET_STOCK PRICE_X_AGE IPAD_TABLET LAPTOP PRINTED VERY_USEFUL INCR_OR_BEGIN AVG_NR_PRODUCTS are jointly insignificant

	Value	df	Probability
F-statistic	1.826691	(16, 26)	0.0834
Likelihood ratio	36.16111	16	0.0027

F-test summary:

	Sum of Sq.	df	Mean Squares
Test SSR	0.094901	16	0.005931
Restricted SSR	0.179323	42	0.004270
Unrestricted SSR	0.084422	26	0.003247

LR test summary:

	Value
Restricted LogL	66.04534
Unrestricted LogL	84.12590

Figure 10.168 – Redundant Variables Test in Eviews – all removed variables - Product LI4

The variables are redundant (probability of 0,0834). This way, although the removed interaction variable Ln Average price per DDD x Ln Detailing flow was significant by itself as described above, it was not when jointly removed with all other discarded variables, which confirms our good decision.

We then analyzed the normality of residuals of our final model regarding product LI4. We selected the option Histogram – Normality Test in the menu option View → Residual Diagnostics, and obtained the output below (figure 10.169):

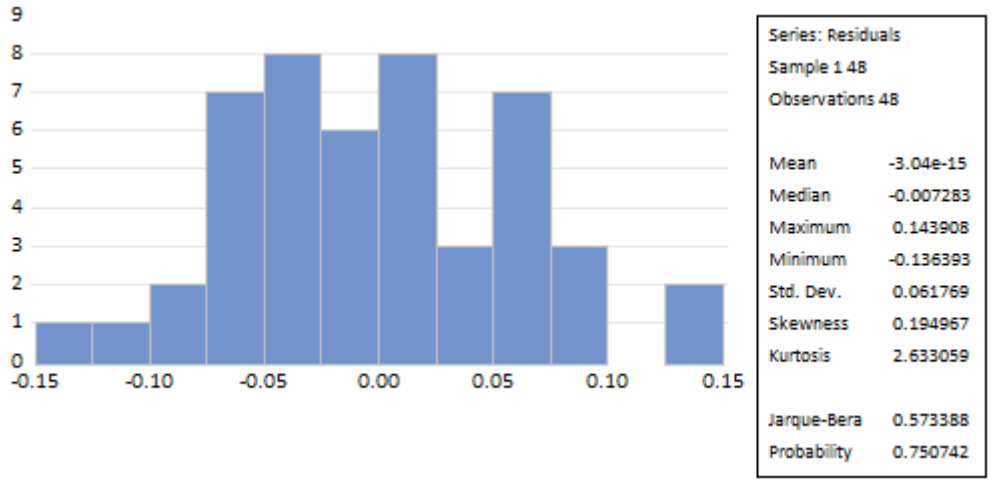
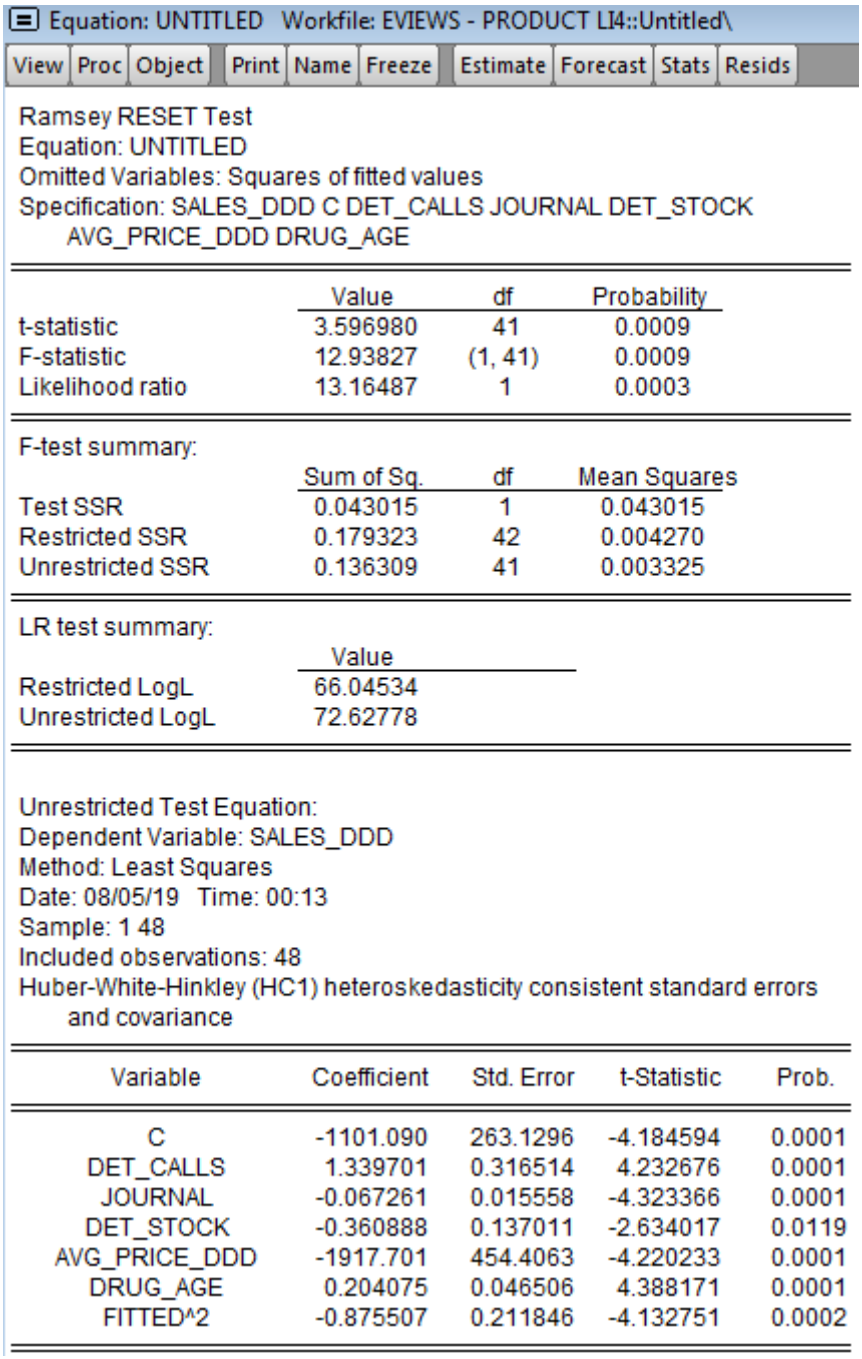


Figure 10.169 – Residuals Normality Test in Eviews – Product LI4

The Jarque-Bera output of 0,573388 means we can not reject the hypothesis of the normality of the residuals ($p > 0,05$).

Finally, we ran the Reset test, by selecting the option Ramsey Reset Test in View → Stability Diagnostics. We ran the analysis (quadratic) and obtained the output shown below (figure 10.170):



Equation: UNTITLED Workfile: EVIEWS - PRODUCT LI4::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Ramsey RESET Test
Equation: UNTITLED
Omitted Variables: Squares of fitted values
Specification: SALES_DDD C DET_CALLS JOURNAL DET_STOCK AVG_PRICE_DDD DRUG_AGE

	Value	df	Probability
t-statistic	3.596980	41	0.0009
F-statistic	12.93827	(1, 41)	0.0009
Likelihood ratio	13.16487	1	0.0003

F-test summary:

	Sum of Sq.	df	Mean Squares
Test SSR	0.043015	1	0.043015
Restricted SSR	0.179323	42	0.004270
Unrestricted SSR	0.136309	41	0.003325

LR test summary:

	Value
Restricted LogL	66.04534
Unrestricted LogL	72.62778

Unrestricted Test Equation:
Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/05/19 Time: 00:13
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-1101.090	263.1296	-4.184594	0.0001
DET_CALLS	1.339701	0.316514	4.232676	0.0001
JOURNAL	-0.067261	0.015558	-4.323366	0.0001
DET_STOCK	-0.360888	0.137011	-2.634017	0.0119
AVG_PRICE_DDD	-1917.701	454.4063	-4.220233	0.0001
DRUG_AGE	0.204075	0.046506	4.388171	0.0001
FITTED^2	-0.875507	0.211846	-4.132751	0.0002

Figure 10.170 – Quadratic Reset Test in Eviews for Product LI4

Since the p-value of the quadratic term is lower than 0,05, the model lacks quadratic terms. We will further address this issue after the analysis of product LI5 in Eviews. We also added a cubic term to the reset test, however obtaining an error ("Near singular matrix error. Regressors may be perfectly collinear").

We then performed the exact same analysis for **product LI5**. Below we find the first screenshot of the coefficients in the first iteration (figure 10.171).

Equation: PRODUCT_LI5 Workfile: EVIEWS - PRODUCT LI5::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/05/19 Time: 13:57
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	33.05748	16.32060	2.025506	0.0536
SALES_DDD_LAG1	-0.072472	0.208341	-0.347853	0.7309
SALES_DDD_LAG2	-0.068772	0.171621	-0.400722	0.6920
DET_CALLS	0.043136	0.449689	0.095925	0.9243
JOURNAL	0.004228	0.004097	1.032062	0.3119
MAILING	-0.006143	0.005575	-1.101829	0.2810
COMPET_GLOBAL	0.086592	0.055706	1.554451	0.1326
DET_STOCK	-2.132489	1.374170	-1.551838	0.1333
OME_STOCK	-0.022417	0.019280	-1.162700	0.2559
COMP_MARK_EXPEND_STOCK	0.273338	0.106592	2.564337	0.0167
AVG_PRICE_DDD	-39.37392	22.85502	-1.722769	0.0973
AVG_COMP_PRICE_DDD	1.405072	0.385712	3.642799	0.0012
DRUG_AGE	-0.134700	0.145528	-0.925598	0.3635
DRUG_AGE_SQ	2.98E-06	0.000505	0.005907	0.9953
PRICE_X_DET	0.054092	0.670763	0.080643	0.9364
PRICE_X_DET_STOCK	3.320159	2.006913	1.654361	0.1106
PRICE_X_AGE	0.237524	0.169283	1.403121	0.1729
IPAD_TABLET	-0.023406	0.185381	-0.126260	0.9005
LAPTOP	-0.434657	0.409112	-1.062440	0.2982
PRINTED	0.124328	0.124924	0.995227	0.3292
VERY_USEFUL	-0.321291	0.215797	-1.488862	0.1490
INCR_OR_BEGIN	0.150913	0.173276	0.870942	0.3921
AVG_NR_PRODUCTS	-0.010094	0.123907	-0.081463	0.9357

R-squared	0.848991	Mean dependent var	11.74742
Adjusted R-squared	0.716102	S.D. dependent var	0.120701
S.E. of regression	0.064312	Akaike info criterion	-2.344141
Sum squared resid	0.103400	Schwarz criterion	-1.447524
Log likelihood	79.25939	Hannan-Quinn criter.	-2.005308
F-statistic	6.388758	Durbin-Watson stat	2.523435
Prob(F-statistic)	0.000011	Wald F-statistic	9.094860
Prob(Wald F-statistic)	0.000000		

Figure 10.171 – Coefficients obtained in eviews – first iteration - product LI5

The sequence of removed variables was the following:

- Drug age squared
- Ln Avg number of products presented during the calls
- Ipad / Tablet (% of times used in calls)
- Ln Sales in DDDs lagged one period
- Ln Sales in DDDs lagged two periods
- Printed material (% of times used in calls)

- Laptop based materials (% of times used in calls)
- Increase / Will begin to prescribe (% of calls)
- Ln Other marketing expenditures stock
- Very useful (% of calls)

Our model was the following (with the significant variables and the ones that are fixed, even non-significant), shown below in figure 10.172:

Equation: PRODUCT_LI5 Workfile: EVIEWS - PRODUCT LI5::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/05/19 Time: 14:11
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	28.95884	8.170896	3.544145	0.0011
DET_CALLS	-0.134931	0.460748	-0.292852	0.7714
JOURNAL	0.002652	0.002946	0.900305	0.3741
MAILING	-0.006223	0.004008	-1.552396	0.1296
COMPET_GLOBAL	0.092167	0.044285	2.081218	0.0448
DET_STOCK	-1.776243	0.861267	-2.062361	0.0467
COMP_MARK_EXPEND_STOCK	0.254279	0.075673	3.360228	0.0019
AVG_PRICE_DDD	-35.54576	11.91259	-2.983881	0.0052
AVG_COMP_PRICE_DDD	1.329876	0.196965	6.751854	0.0000
DRUG_AGE	-0.126900	0.032235	-3.936682	0.0004
PRICE_X_DET	0.283566	0.676656	0.419070	0.6777
PRICE_X_DET_STOCK	2.795227	1.218650	2.293707	0.0279
PRICE_X_AGE	0.225780	0.047187	4.784834	0.0000

R-squared	0.809488	Mean dependent var	11.74742
Adjusted R-squared	0.744170	S.D. dependent var	0.120701
S.E. of regression	0.061050	Akaike info criterion	-2.528434
Sum squared resid	0.130448	Schwarz criterion	-2.021650
Log likelihood	73.68242	Hannan-Quinn criter.	-2.336920
F-statistic	12.39295	Durbin-Watson stat	2.705920
Prob(F-statistic)	0.000000	Wald F-statistic	11.28422
Prob(Wald F-statistic)	0.000000		

Figure 10.172 – Coefficients obtained in eviews – after manual removal of variables - product LI5

Next, we looked at the VIFs of these variables, given our suspicion of multicollinearity originated by the interaction variables Ln Average drug price per DDD x Ln Detailing flow, Ln Average drug price per DDD x Ln Detailing stock, and Ln Average drug price per DDD x Drug age. The output is shown below in fiture 10.173.

Equation: PRODUCT_LI5 Workfile: EVIEWS - PRODUCT LI5::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

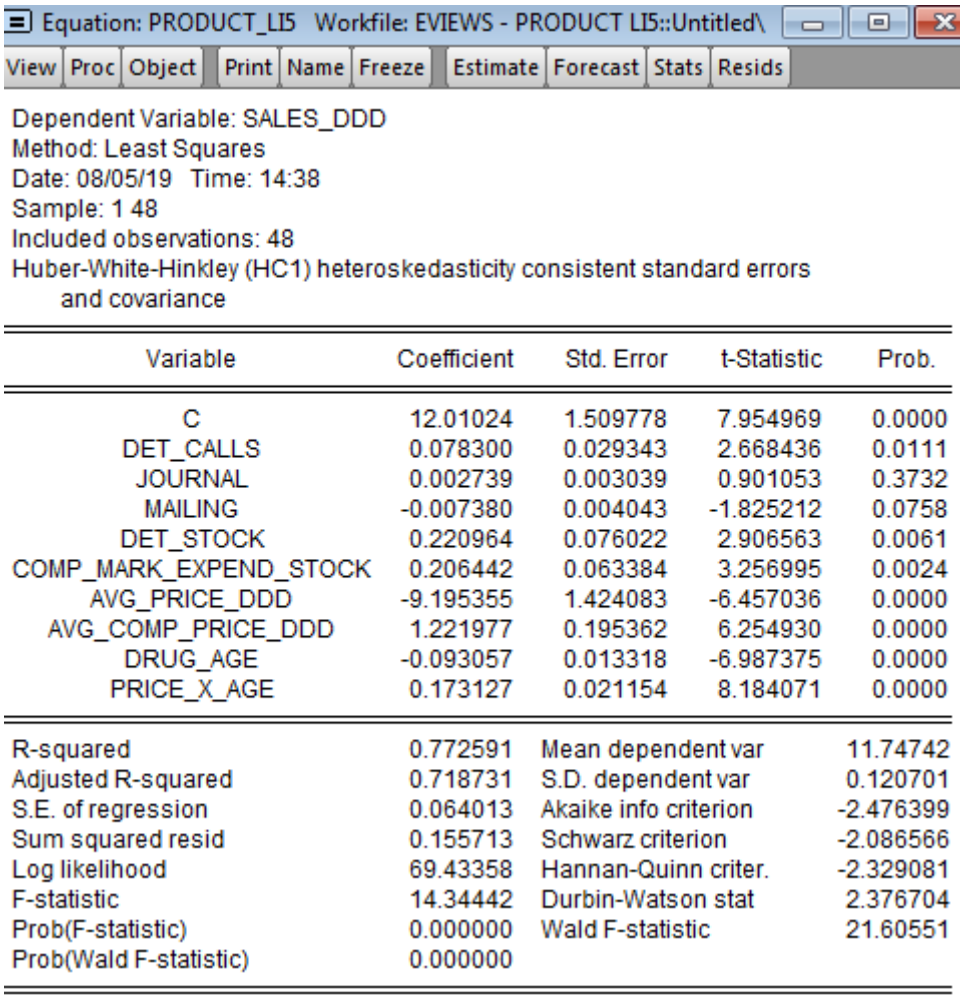
Variance Inflation Factors
Date: 08/05/19 Time: 14:17
Sample: 1 48
Included observations: 48

Variable	Coefficient Variance	Uncentered VIF	Centered VIF
C	66.76354	1100921.	NA
DET_CALLS	0.212288	172697.7	916.2629
JOURNAL	8.68E-06	4.291634	2.444479
MAILING	1.61E-05	3.313964	2.464744
COMPET_GLOBAL	0.001961	4796.634	6.921466
DET_STOCK	0.741780	788779.5	2173.489
COMP_MARK_EXPE...	0.005726	16276.46	11.11559
AVG_PRICE_DDD	141.9098	1091442.	9357.958
AVG_COMP_PRICE_...	0.038795	90.37220	86.13302
DRUG_AGE	0.001039	31757.08	2894.433
PRICE_X_DET	0.457863	177654.8	4460.191
PRICE_X_DET_STOCK	1.485109	751567.9	15777.97
PRICE_X_AGE	0.002227	28451.64	1596.247

Figure 10.173 – VIFs for product LI5 with Eviews

We proceeded by removing Ln Average drug price per DDD x Ln Detailing stock. We then removed Ln Competitive marketing expenditures flow (which had meanwhile became non-significant), and computed the VIFs again and noted that the VIF of the interaction variable Ln Average drug price per DDD x Ln Detailing flow was 4068,516. We then removed this variable and ran the VIFs again, which resulted in very high values in three variables: Drug age (539,81), Ln Average drug price per DDD (138,59), and the interaction variable Ln Average drug price per DDD x Drug age (361,53). By removing this last interaction variable, the significance and signals of most of the variables became less logic. Therefore, we opted by keeping the variable in the equation, despite the very high VIFs.

Our final model is thefore the following (figure 10.174):



Equation: PRODUCT_LI5 Workfile: EVIEWS - PRODUCT LI5::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/05/19 Time: 14:38
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	12.01024	1.509778	7.954969	0.0000
DET_CALLS	0.078300	0.029343	2.668436	0.0111
JOURNAL	0.002739	0.003039	0.901053	0.3732
MAILING	-0.007380	0.004043	-1.825212	0.0758
DET_STOCK	0.220964	0.076022	2.906563	0.0061
COMP_MARK_EXPEND_STOCK	0.206442	0.063384	3.256995	0.0024
AVG_PRICE_DDD	-9.195355	1.424083	-6.457036	0.0000
AVG_COMP_PRICE_DDD	1.221977	0.195362	6.254930	0.0000
DRUG_AGE	-0.093057	0.013318	-6.987375	0.0000
PRICE_X_AGE	0.173127	0.021154	8.184071	0.0000

R-squared	0.772591	Mean dependent var	11.74742
Adjusted R-squared	0.718731	S.D. dependent var	0.120701
S.E. of regression	0.064013	Akaike info criterion	-2.476399
Sum squared resid	0.155713	Schwarz criterion	-2.086566
Log likelihood	69.43358	Hannan-Quinn criter.	-2.329081
F-statistic	14.34442	Durbin-Watson stat	2.376704
Prob(F-statistic)	0.000000	Wald F-statistic	21.60551
Prob(Wald F-statistic)	0.000000		

Figure 10.174 – Coefficients obtained in Eviews – final interaction – product LI5

Next, we ran a Redundant Variable Test (figure 10.175) considering the full model and the simultaneous removal of all the variables we listed above. The variables are redundant (probability of 0,5014).

Equation: PRODUCT_LI5 Workfile: EVIEWS - PRODUCT LI5::Untitled\

View | Proc | Object | Print | Name | Freeze | Estimate | Forecast | Stats | Resids

Redundant Variables Test
Equation: PRODUCT_LI5
Redundant variables: SALES_DDD_LAG1 SALES_DDD_LAG2 COMPET_GLOBAL OME_STOCK DRUG_AGE_SQ PRICE_X_DET PRICE_X_DET_STOCK IPAD_TABLET LAPTOP PRINTED VERY_USEFUL INCR_OR_BEGIN AVG_NR_PRODUCTS
Specification: SALES_DDD C SALES_DDD_LAG1 SALES_DDD_LAG2 DET_CALLS JOURNAL MAILING COMPET_GLOBAL DET_STOCK OME_STOCK COMP_MARK_EXPEND_STOCK AVG_PRICE_DDD AVG_COMP_PRICE_DDD DRUG_AGE DRUG_AGE_SQ PRICE_X_DET PRICE_X_DET_STOCK PRICE_X_AGE IPAD_TABLET LAPTOP PRINTED VERY_USEFUL INCR_OR_BEGIN AVG_NR_PRODUCTS
Null hypothesis: SALES_DDD_LAG1 SALES_DDD_LAG2 COMPET_GLOBAL OME_STOCK DRUG_AGE_SQ PRICE_X_DET PRICE_X_DET_STOCK IPAD_TABLET LAPTOP PRINTED VERY_USEFUL INCR_OR_BEGIN AVG_NR_PRODUCTS are jointly insignificant

	Value	df	Probability
F-statistic	0.972936	(13, 25)	0.5018
Likelihood ratio	19.65161	13	0.1042

F-test summary:

	Sum of Sq.	df	Mean Squares
Test SSR	0.052313	13	0.004024
Restricted SSR	0.155713	38	0.004098
Unrestricted SSR	0.103400	25	0.004136

LR test summary:

	Value
Restricted LogL	69.43358
Unrestricted LogL	79.25939

Figure 10.175 – Redundant Variables Test in Eviews – all removed variables - Product LI5

The next step was the analysis of the normality of residuals of our final model regarding product LI5, obtaining the output below (figure 10.176):

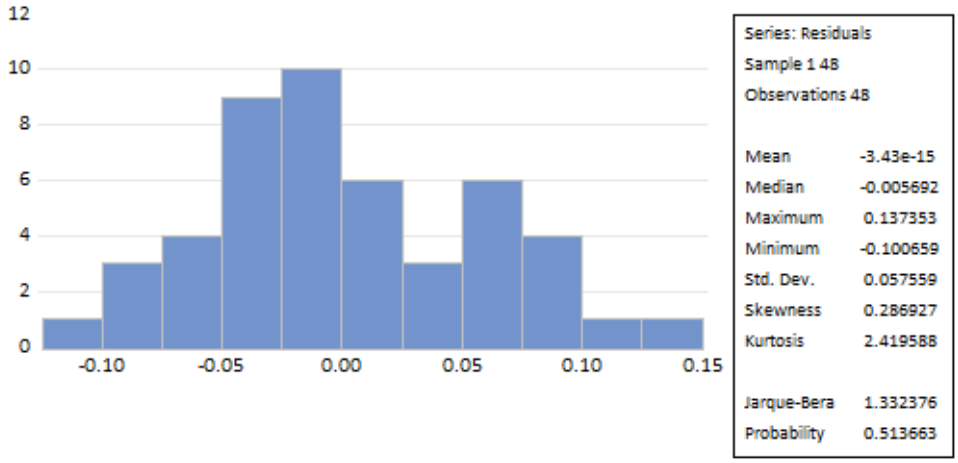


Figure 10.176 – Residuals Normality Test in Eviews – Product LI5

With a Jarque-Bera output of 0,513663, there is no evidence to suggest that the residuals do not follow a normal distribution.

Finally, we ran the quadratic and cubic Reset test (figure 10.177).

Ramsey RESET Test
Equation: PRODUCT_LI5
Omitted Variables: Squares of fitted values
Specification: SALES_DDD C DET_CALLS JOURNAL MAILING DET_STOCK COMP_MARK_EXPEND_STOCK AVG_PRICE_DDD AVG_COMP_PRICE_DDD DRUG_AGE PRICE_X_AGE

	Value	df	Probability
t-statistic	1.822567	37	0.0765
F-statistic	3.321750	(1, 37)	0.0765
Likelihood ratio	4.126709	1	0.0422

F-test summary:

	Sum of Sq.	df	Mean Squares
Test SSR	0.012828	1	0.012828
Restricted SSR	0.155713	38	0.004098
Unrestricted SSR	0.142885	37	0.003862

LR test summary:

	Value
Restricted LogL	69.43358
Unrestricted LogL	71.49694

Unrestricted Test Equation:
Dependent Variable: SALES_DDD
Method: Least Squares
Date: 08/05/19 Time: 14:50
Sample: 1 48
Included observations: 48
Huber-White-Hinkley (HC1) heteroskedasticity consistent standard errors and covariance

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	157.2769	73.34623	2.144308	0.0386
DET_CALLS	1.916984	0.930311	2.060584	0.0464
JOURNAL	0.068377	0.033742	2.026465	0.0500
MAILING	-0.179930	0.086974	-2.068780	0.0456
DET_STOCK	5.316133	2.559226	2.077242	0.0448
COMP_MARK_EXPEND_STOCK	5.063817	2.448386	2.068227	0.0457
AVG_PRICE_DDD	-225.2281	109.0715	-2.064958	0.0460
AVG_COMP_PRICE_DDD	30.03069	14.55203	2.063678	0.0461
DRUG_AGE	-2.275806	1.101885	-2.065375	0.0459
PRICE_X_AGE	4.231826	2.048098	2.066223	0.0459
FITTED^2	-1.002348	0.504661	-1.986180	0.0545

Figure 10.177 – Quadratic Reset Test in Eviews for Product LI5

Since the p-value of the quadratic term is higher than 0,05, the model does not appear to lack quadratic terms. When we performed the cubic Reset test we obtained the same error message as with product LI4 (“Near singular matrix error. Regressors may be perfectly collinear”).

Having solved the heterocedasticity issues, we faced a more serious problem: 10 out of the 15 products analyzed did not pass the Reset test, which tests for the good specification of the model.

Table 10.89 below explicits the p-values of the Reset test in the two columns on the right, for both quadratic and cubic terms. All these outputs were calculated using SPSS, except for products LI4 and LI5.

Table 10.89 – Summary of issues detected in Model 8.4

	VIFs (when ≥ 10)										Shapiro-Wilk Sig. (when ≤ 5%)	Heteroceda sticity: ANOVA Sig. (when ≤ 5%)	Reset test p-value (when ≤ 5%)	
Product	Ln Sales in DDDs lagged one period	Ln Sales in DDDs lagged two periods	Ln Detailing stock (calls)	Ln Competitive global marketing expenditures stock	Ln Average drug price per DDD	Ln Average competitors price per DDD	Ln Detailing stock (calls)	Drug age	Drug age squared	Drug price x Drug age			Quadratic	Cubic
BL1	---	---	---	---	23,987	---	12,953	12,607	---	---	---	---	---	---
BL2	---	23,672	---	---	18,146	---	---	---	---	---	---	---	---	---
PA1	---	---	---	---	---	---	---	---	---	---	---	---	4,2%	4,3%
PA2	---	---	---	---	10,924	---	---	14,032	---	---	---	---	1,4%	1,4%
PA3	---	---	---	---	11,531	---	---	232,508	162,796	---	---	---	0,0%	0,0%
PA5	---	---	---	14,593	13,487	---	---	---	---	---	---	---	0,4%	0,4%
HE1	---	---	---	---	13,613	---	---	25,956	---	---	---	---	0,0%	0,0%
HE2	---	---	---	---	---	---	---	---	---	---	---	---	---	---
HE3	---	---	---	---	10,953	---	---	11,069	---	---	---	---	0,0%	0,0%
HE4	32,509	35,352	---	---	---	---	---	10,218	---	---	0,033	---	0,0%	0,0%
LI1	---	---	---	---	---	---	---	---	---	---	---	---	---	---
LI2	---	---	---	---	---	11,716	---	12,927	---	---	---	---	0,1%	0,1%
LI3	---	---	---	---	---	---	---	---	---	---	---	---	0,9%	0,9%
LI4	---	---	---	---	22,407	---	---	30,580	---	---	---	--- (Eviews)	0,9%	N/A
LI5	---	---		---	138,594	82,752	16,200	539,814	---	361,529	---	--- (Eviews)	---	N/A

In order to investigate the origin of the Reset test issues, we tried to find, among the variables used in Model 8.4 – and before the removal of eventual variables due to extremely high VIFs, the origin of the non-linearity. To do this, we activated, in the regressions, the option "Produce all partial plots" in Plots, in SPSS. We started with product PA3, the first we detected with strong problems with (PA1 had a p-value of 0,042 and PA2 had 0,014, whereas PA3 had 0,000001. The outputs are shown below (figures 10178, 10.179, 10.180, 10.181, 10.182, 10.183, 10.184, 10.185 and 10.186).

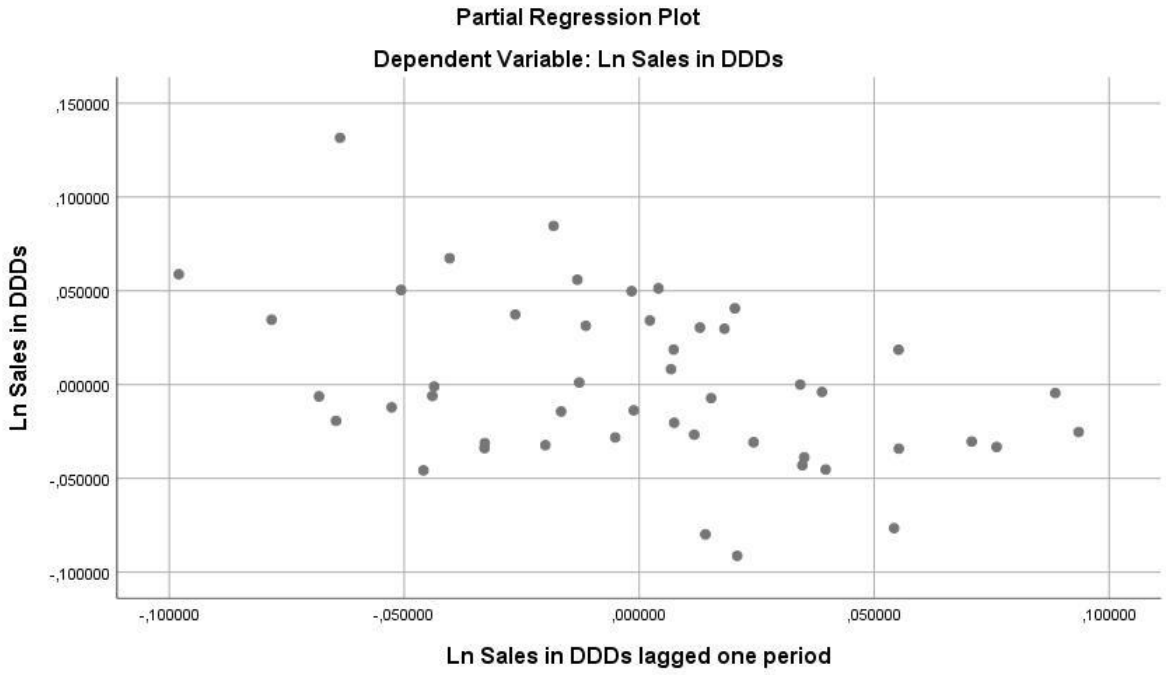


Figure 10.178 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Ln Sales in DDDs lagged one period

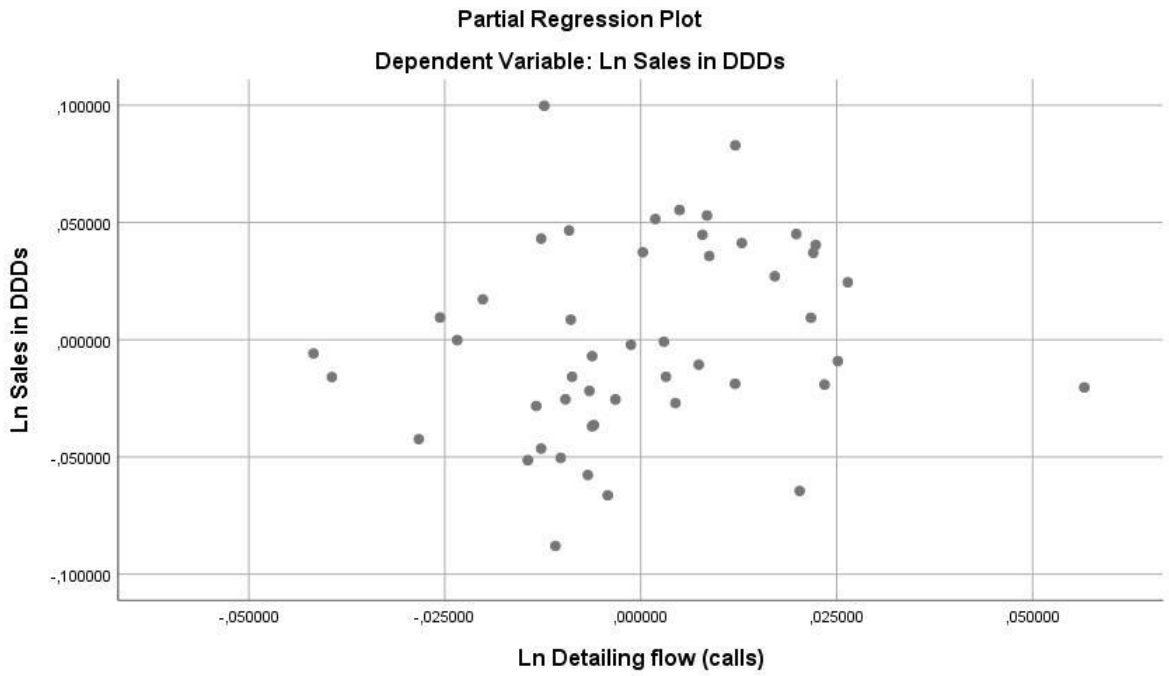


Figure 10.179 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Ln Detailing flow

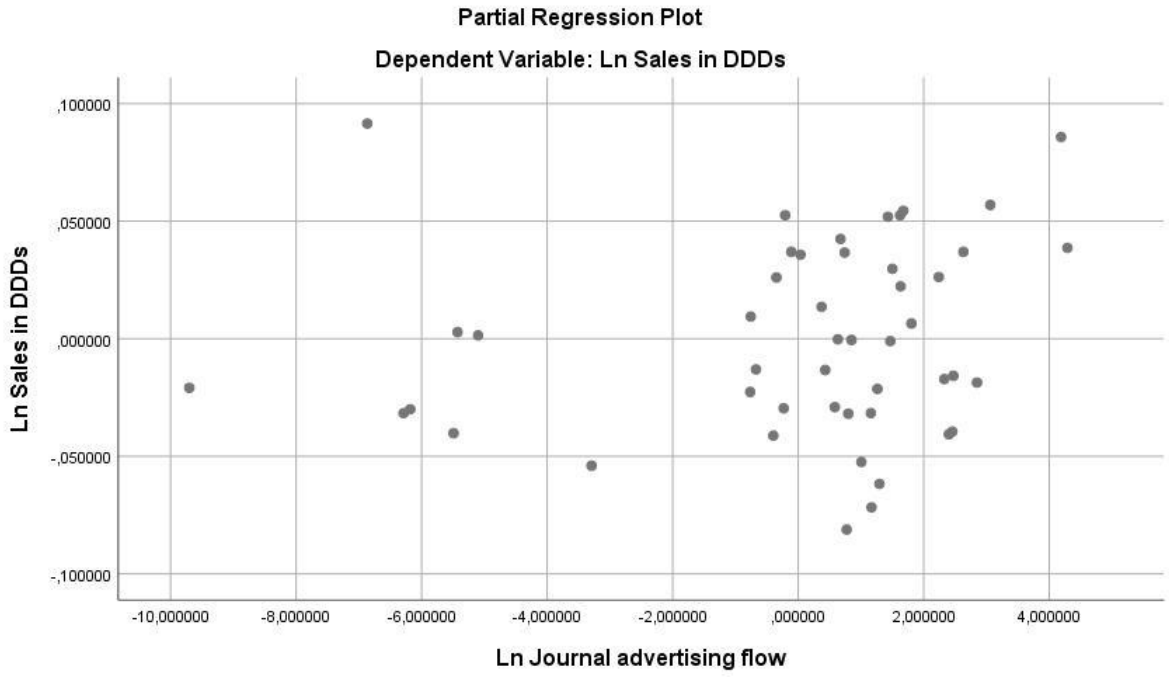


Figure 10.180 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Ln Journal advertising flow

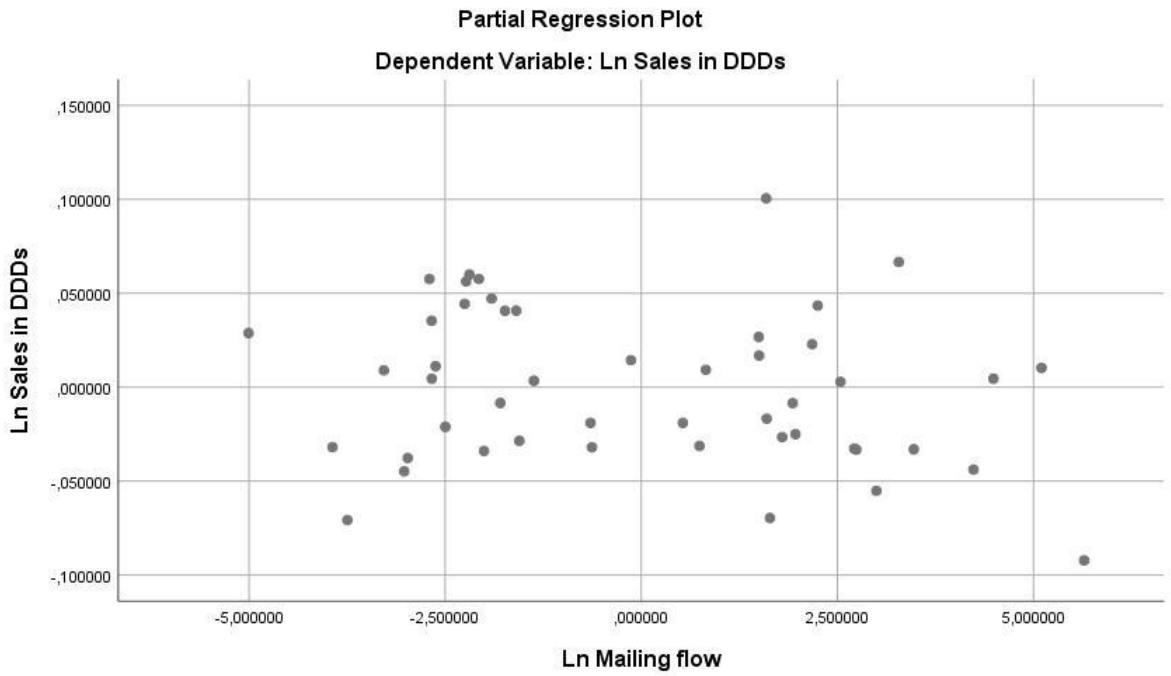


Figure 10.181 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Ln Mailing flow

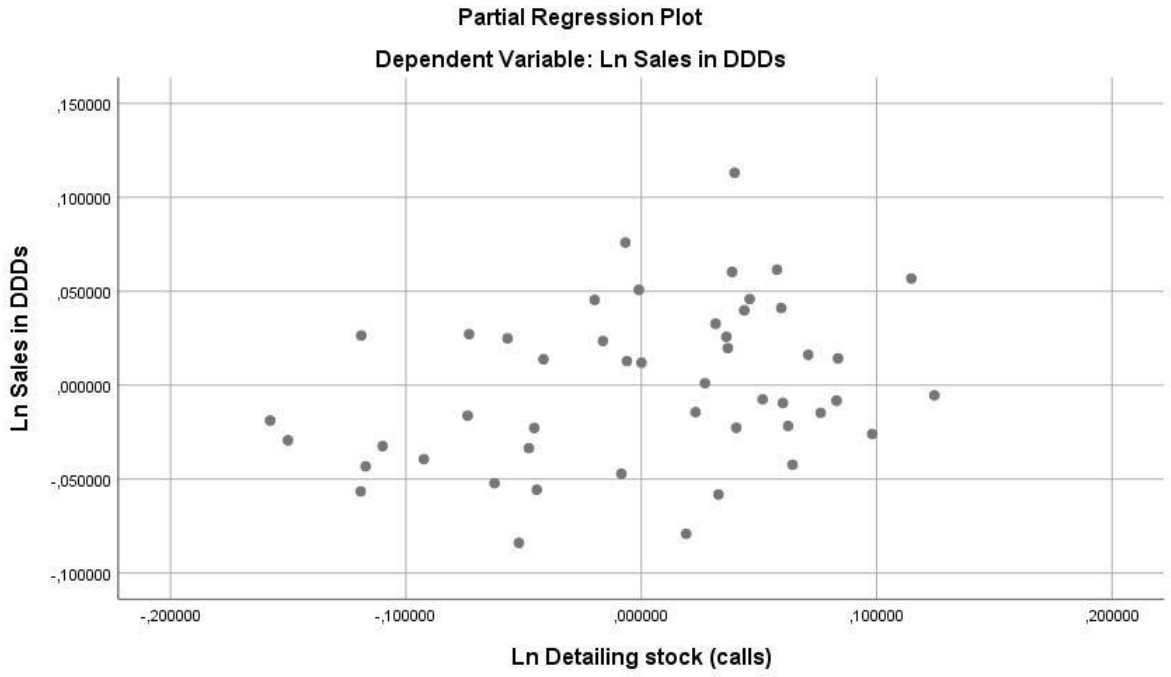


Figure 10.182 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Ln Detailing stock (calls)

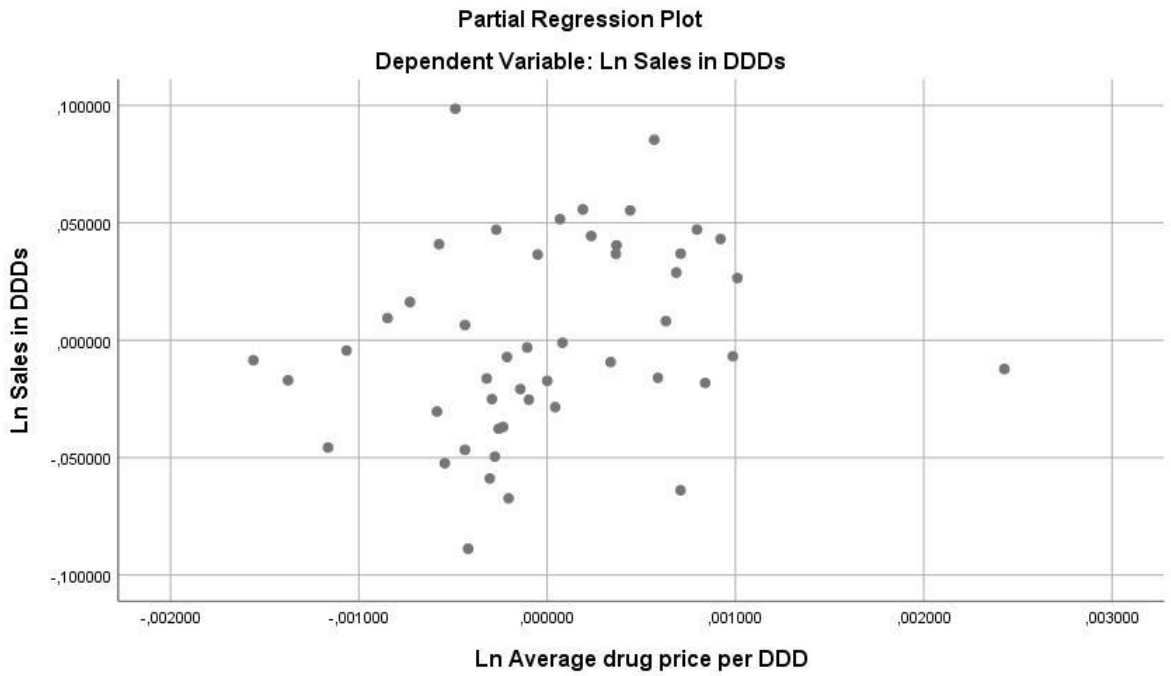


Figure 10.183 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Ln Average drug price per DDD

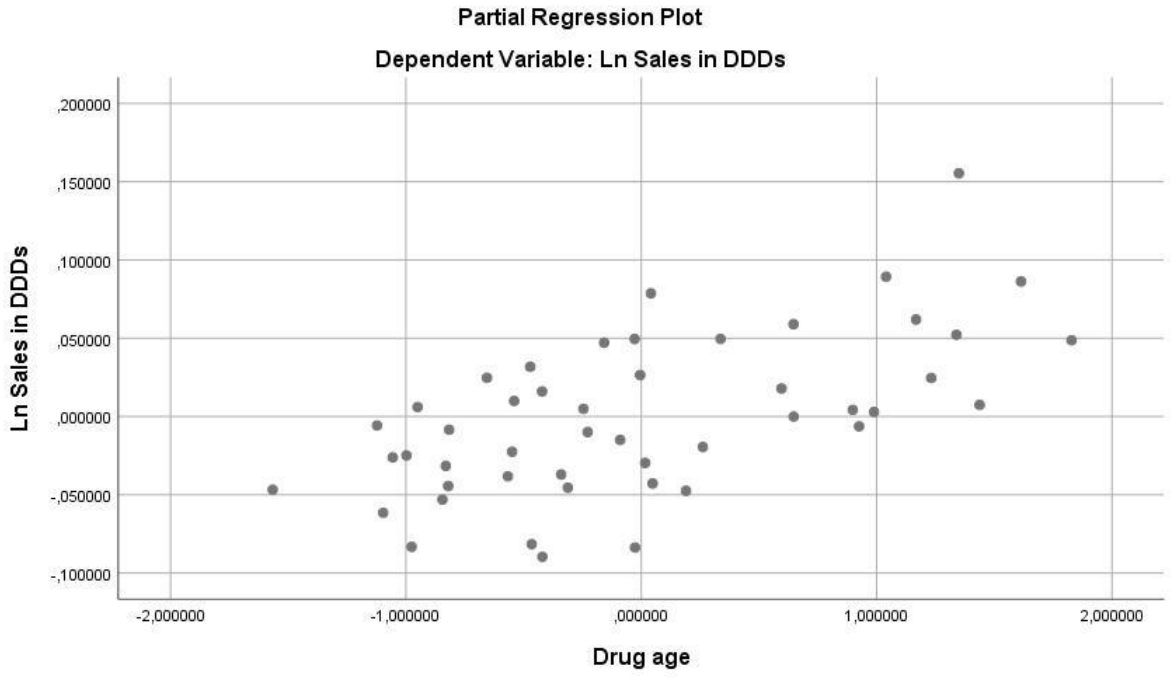


Figure 10.184 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Drug age

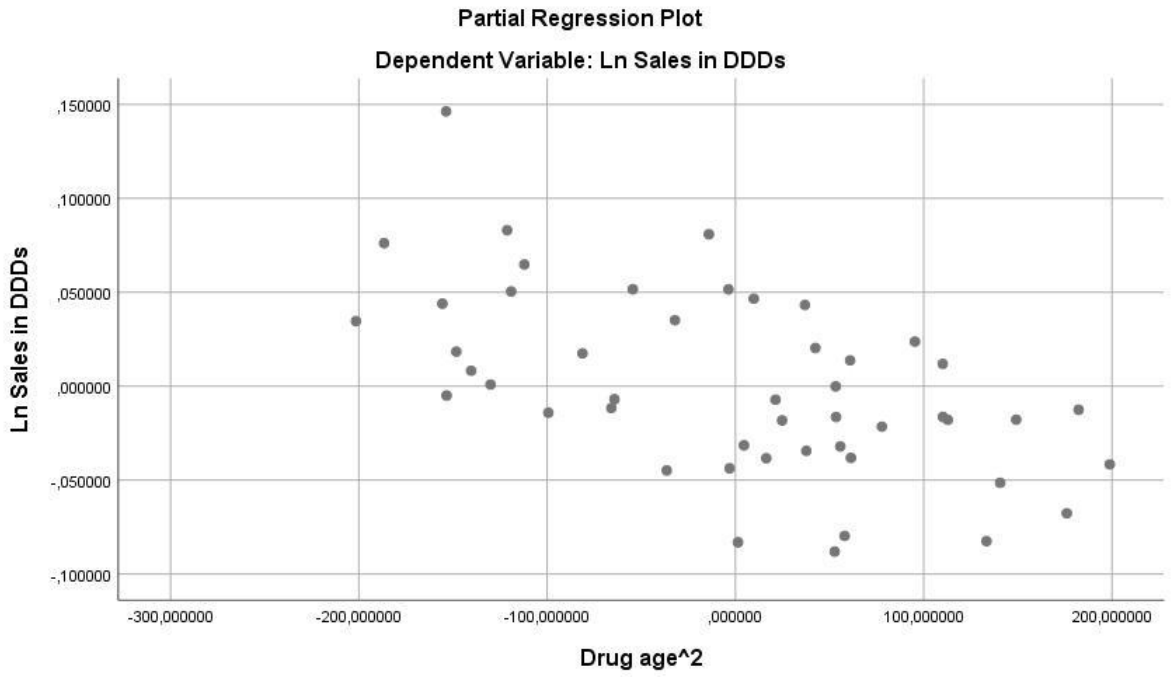


Figure 10.185 – Partial Regression Plot for product BL1 in Model 8.4 – Ln Sales in DDDs vs Drug age^2

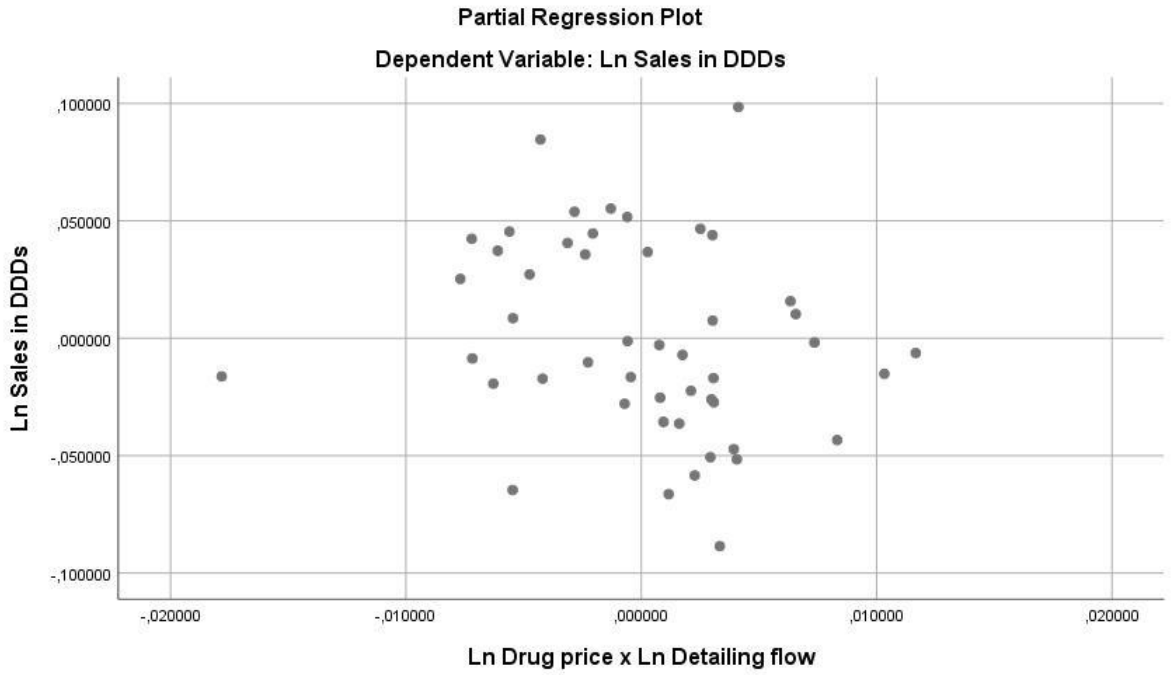


Figure 10.186 – Partial Regression Plot for product PA3 in Model 8.4 – Ln Sales in DDDs vs Ln Drug price x Ln Detailing flow

Based on the charts listed above, there was hardly any evident source of non-linearity in all the independent variables, except perhaps the variables Ln Detailing flow (calls), Ln Journal advertising flow, Ln Mailing flow, and Ln Average drug price per DDD (all with eventual signs of non-linearity). To perform a test, we ran one additional regression and performed the correspondent Reset tests, adding the variables:

- Ln Detailing flow x Ln Detailing flow
- Ln Journal advertising flow x Ln Journal advertising flow
- Ln Mailing flow x Ln Mailing flow
- Ln Average drug price per DDD x Ln Average drug price per DDD

After computing the new variables, we ran the regression saving the unstandardized predicted values, squared and cubed them, and ran two regressions again. The reset test did not pass, again:

- The quadratic unstandardized predicted values coefficient had a p-value of 0,001014
- The cubic unstandardized predicted values coefficient had a p-value of 0,000997

So that we could exclude the situation where product PA3 could be an "outlier" presenting a very unique behavior, we ran this analysis also for HE1, the next product with the lowest p-value in the reset test (0,000001 in the quadratic coefficient and 0,000001 in the cubed coefficient). We show the outputs in figures 10.187, 10.188, 10.189, 10.190, 10.191, 10.192, 10.193, 10.194 and 10.195.

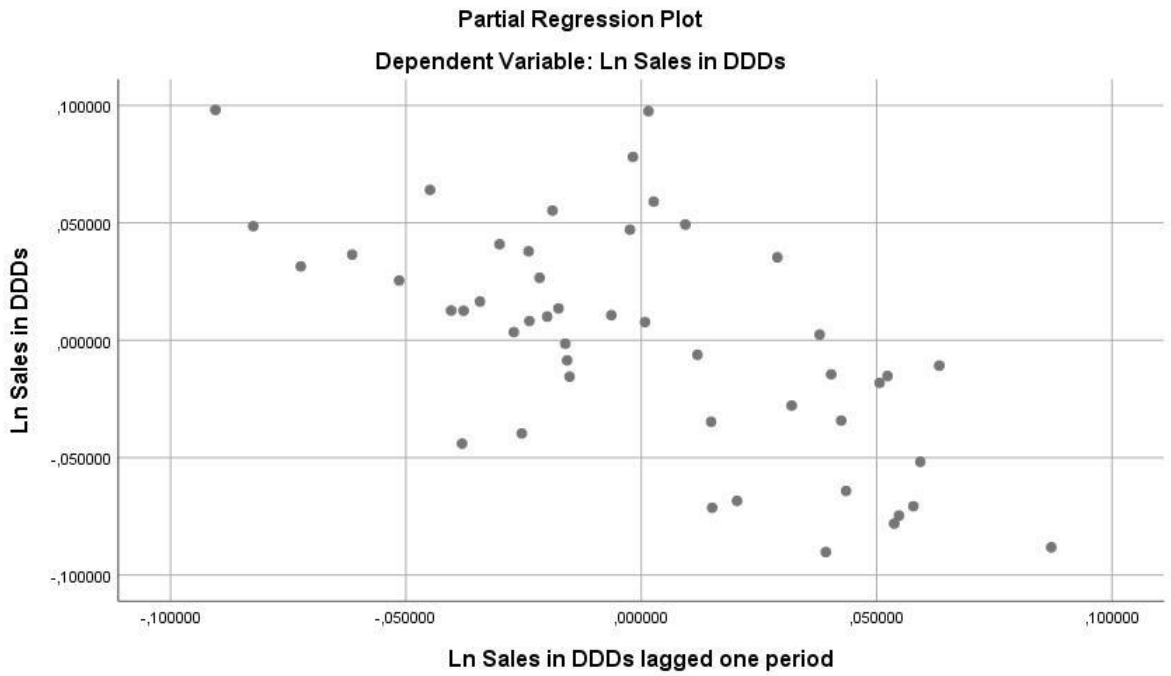


Figure 10.187 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Ln Sales in DDDs lagged one period

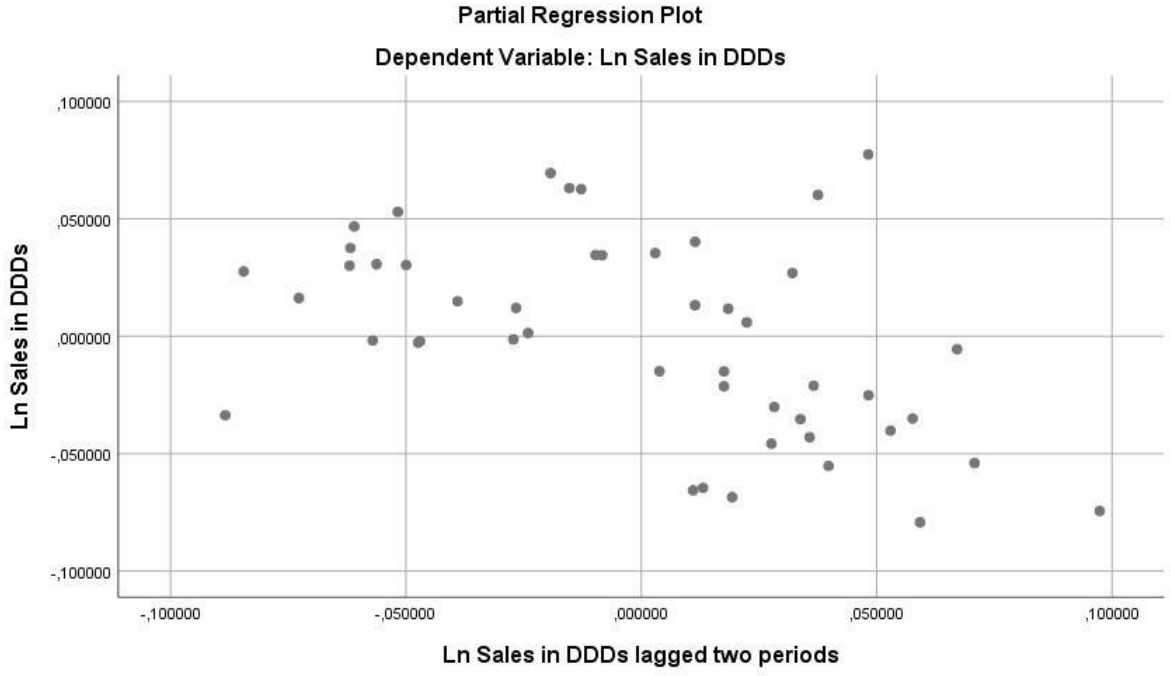


Figure 10.188 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Ln Sales in DDDs lagged two periods

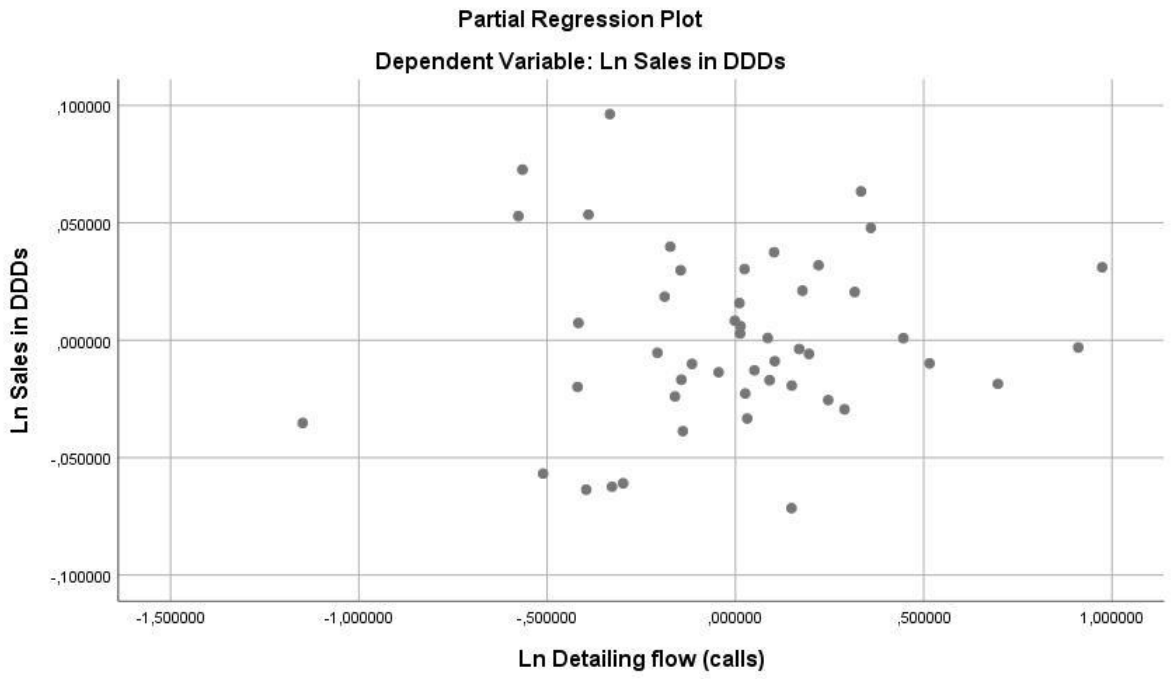


Figure 10.189 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Ln Detailing flow

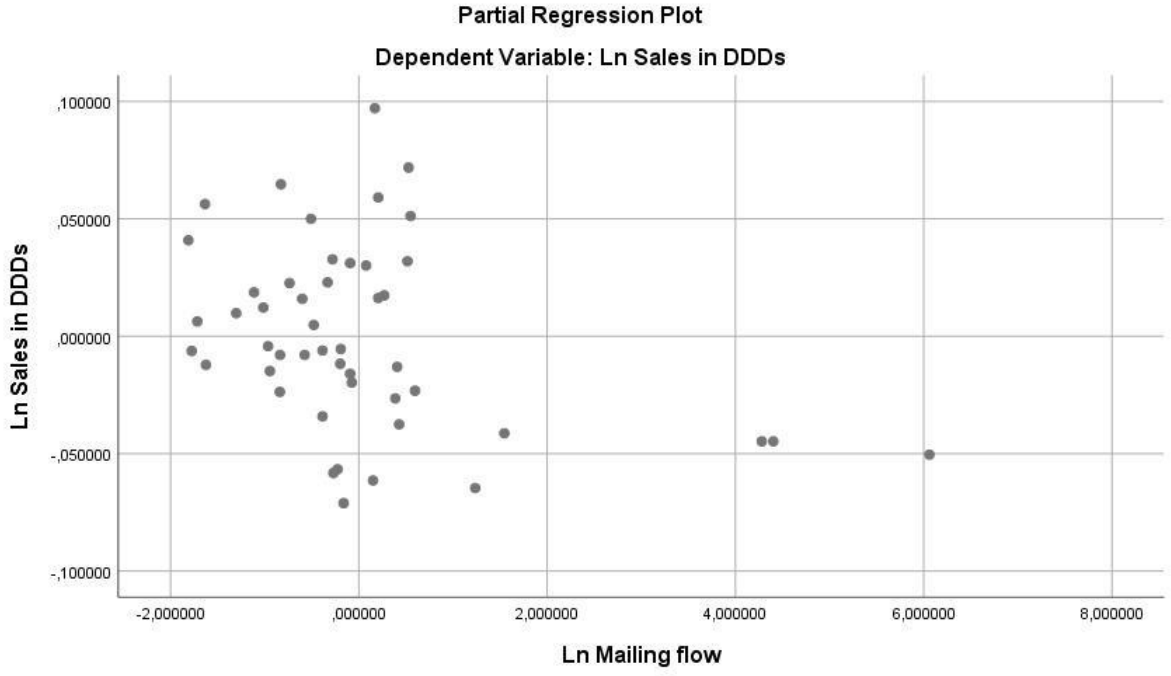


Figure 10.190 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Ln Mailing flow

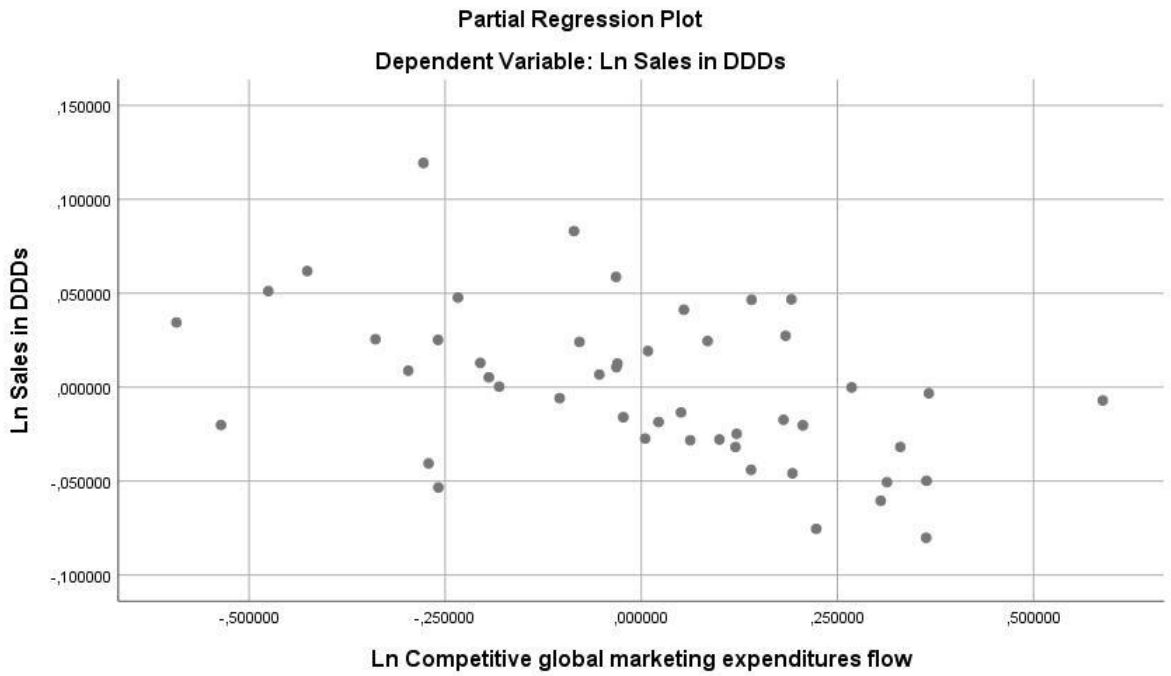


Figure 10.191 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Ln Competitive global marketing expenditures flow

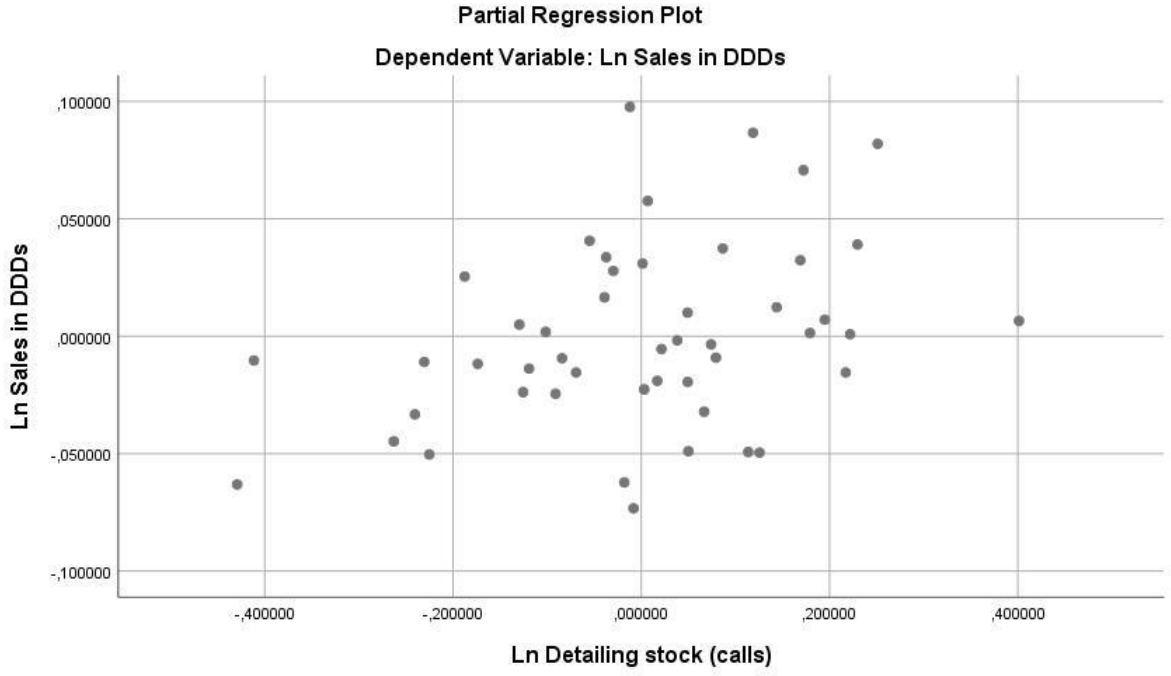


Figure 10.192 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Ln Detailing stock

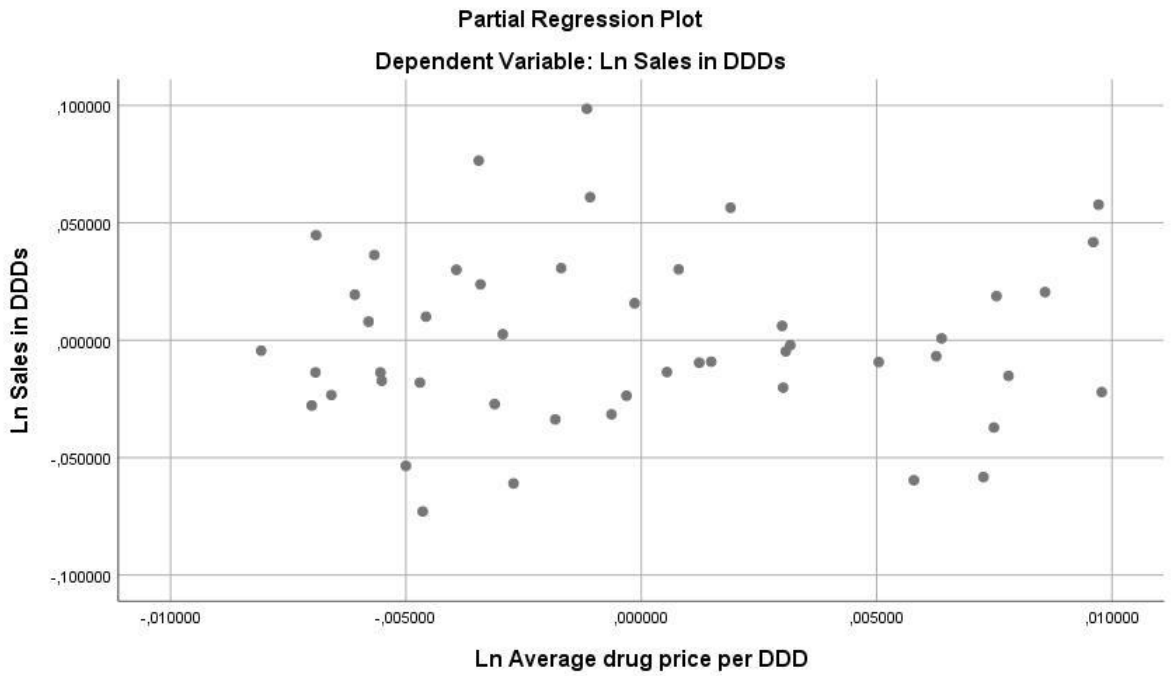


Figure 10.193 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Ln Average drug price per DDD

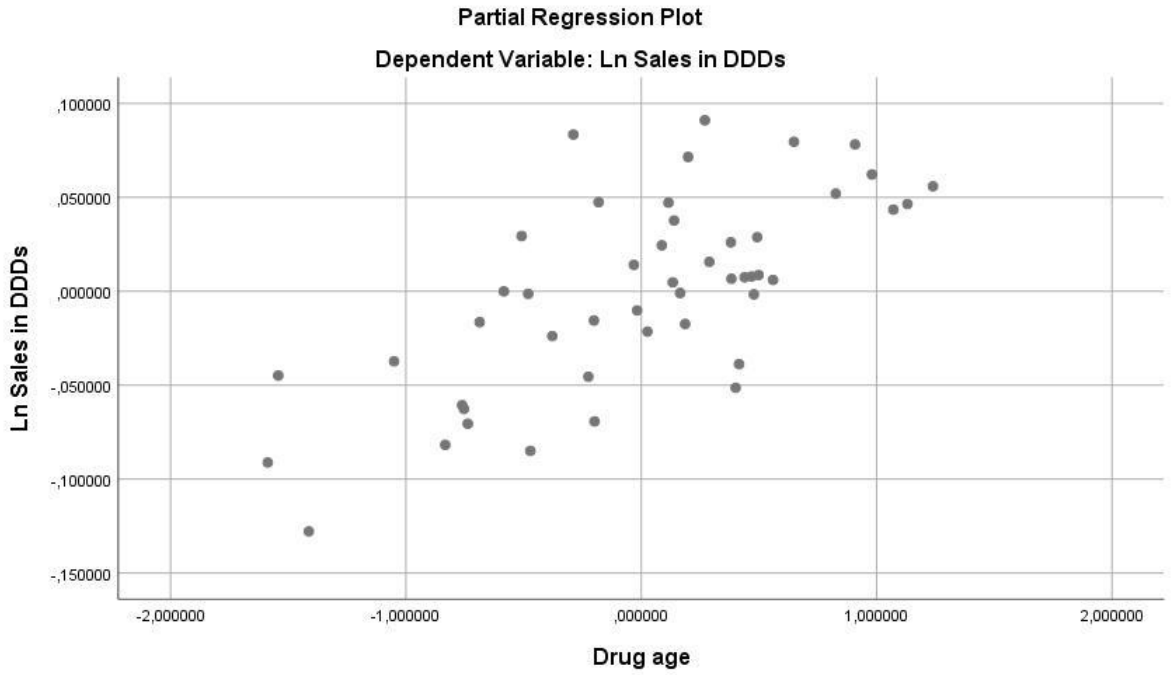


Figure 10.194 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Drug age

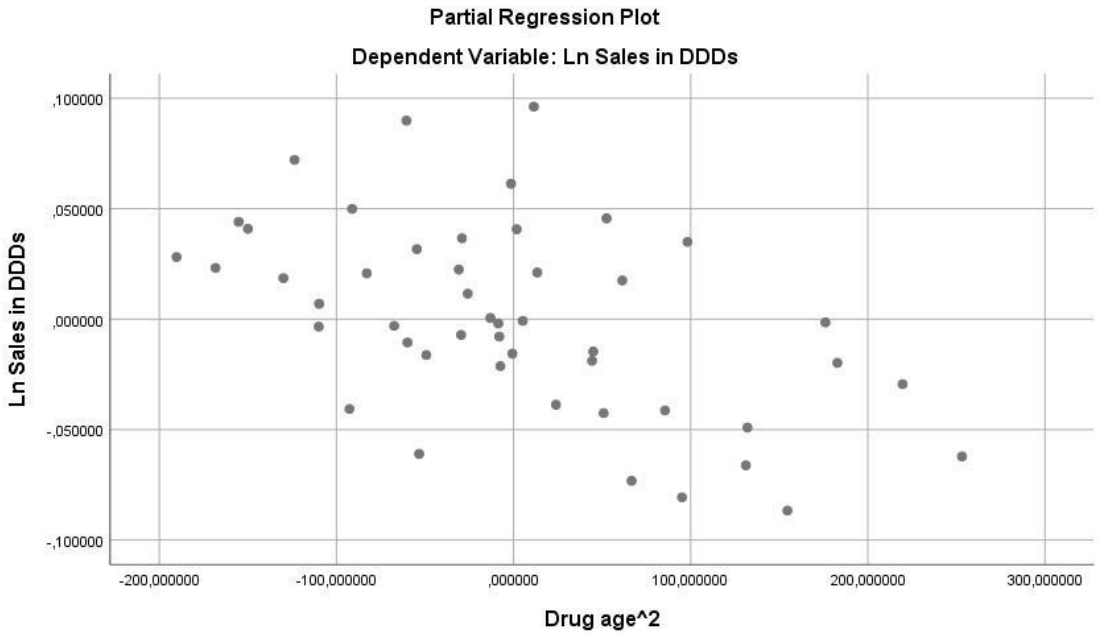


Figure 10.195 – Partial Regression Plot for product HE1 in Model 8.4 – Ln Sales in DDDs vs Drug age^2

In the case of HE1, we could find some evidences of non-linearity in the variables Ln Sales in DDDs lagged two periods, Ln Mailing flow, and Ln Competitive global marketing expenditures flow. To perform a test, we ran one additional regression and performed the correspondent Reset tests, adding the variables:

- Ln Sales in DDDs lagged two periods x Ln Sales in DDDs lagged two periods
- Ln Mailing flow x Ln Mailing flow
- Ln Competitive global marketing expenditures flow x Ln Competitive global marketing expenditures flow

The reset test did not pass, again:

- The quadratic unstandardized predicted values coefficient had a p-value of 0,000001
- The cubic unstandardized predicted values coefficient had a p-value of 0,000001

The endeavors made to find the non-linearity in the relation between the dependent and the independent variables did not produce results in these two products. The non-linearity is relevant and in order to evaluate our options, we considered several important aspects:

- There are more than 20 independent variables in Model 8.4
- We are analyzing 15 eligible products

- We used the main interaction and quadratic variables suggest by the theory of pharmaceutical marketing
- There must be transformations in the variables that would allow the Reset test to pass, but we do not know which. It would be extremely time consuming to run all the combinations of interactions, squared and cubic terms of all variables, with no guarantee of success
- Our percentage of products with misspecification (10 out of 15, or 66,6%) is aligned with results obtained by Wieringa & Leeflang (2013) in their research using similar data (between 51% and 92% misspecified products, with an average of 76% in the seven models tested). If we consider only the products with a Reset test p-value lower than 1%, then the percentage of our products with misspecification drops to 53,3% (8 out of 15)

Given all the above points, we decided to continue our analysis, further investigating Model 8.4. The updated summary of good specification (after running LI4 and LI5 equations with Eviews) is shown in table 10.90 below.

Table 10.90 – Summary of the good specification analysis – Model 8.after the use of Eviews in products LI4 and LI5

		Blood		Pancreas				Heart				Liver				
		BL1	BL2	PA1	PA2	PA3	PA5	HE1	HE2	HE3	HE4	LI1	LI2	LI3	LI4	LI5
Collinearity diagnostics	All VIFs < 10?	No	No	Yes	No	No	No	No	Yes	No	No	Yes	No	Yes	No	No
Normality of residuals	| Skewness | < 0.5?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
	| Kurtosis | < 0.5?	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	No
	Shapiro-Wilk Sig. > 0.05?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Homocedasticity diagnostics	ANOVA | Jarque-Bera Sig. > 0.05?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	---	---
Reset test	Quadratic coeff. Sig. > 0.05?	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes
	Cubic coeff. Sig. > 0.05?	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No	N/A	N/A

10.6.4.2. Results

It is now time to refresh the table with the summary of coefficients in Model 8.4, after using Eviews in the case of products LI4 and LI5 (table 10.91).

Table 10.91 – Summary of coefficients in Model 8.4 – after using Eviews in products LI4 and LI5

			Older	Younger	Older	Older	Younger	Younger	Older	Older	Older	Older	Older	Older	Older	Younger	Younger
			BL1	BL2	PA1	PA2	PA3	PA5	HE1	HE2	HE3	HE4	LI1	LI2	LI3	LI4	LI5
Constant			-2,507	6,454	12,529	18,402	15,835	6,294	19,188	14,336	22,192	-0,817	16,977	26,458	12,752	-38,519	12,010
Lagged sales	Ln Sales in DDDs lagged one period					-0,360	-0,402		-0,377			0,518		-0,564			
	Ln Sales in DDDs lagged two periods			0,585								0,487		-0,350			
Marketing expenditures flow	**Own**	Ln Detailing flow	-0,205	0,063	0,032	0,002	-0,027	0,058	-0,001	0,024	-0,011	0,025	-0,023	0,010	0,019	0,054	0,078
		Ln Journal advertising flow	0,005	0,005	0,000	0,003	0,002	0,001		0,006			0,001	-0,001	0,008	-0,003	0,003
		Ln Direct marketing flow	0,001	0,002	-0,004	-0,001	-0,004	-0,006		-0,002	0,014		-0,005				-0,007
	Competitive	Ln Competitive marketing expenditures flow	0,136														
Marketing expenditures stock	**Own**	Ln Detailing stock	0,165	-0,011	0,195	0,076	0,214	-0,049	0,099	-0,082	0,053	0,018	-0,112	0,031	0,093	-0,010	0,221
		Ln Other marketing expenditures stock															
	Competitive	Ln Competitive global marketing expenditures stock	0,631					0,406									0,206
Price	**Own**	Ln Average drug price per DDD	-0,642	-1,471	-0,897	-0,637	1,475	1,675	1,048	-0,279	-1,769	-0,268	0,672	-1,903	-1,826	-78,24	-9,195
	Competitors	Ln Average competitors drug price per DDD								-0,348	5,078			0,232			1,222
Drug age	Drug age		0,080	0,002	0,003	0,005	0,041	0,009	0,015		-0,030	0,002	-0,002	-0,001	-0,003	0,008	-0,093
	Drug age squared						-0,0003										
Marketing expenditures interactions	Ln Drug price x Ln Detailing flow																
	Ln Drug price x Ln Detailing stock																
	Ln Drug price x drug age																0,173
Additional variables	Ipad / Tablet (% of times used in calls)										0,198						
	Laptop based materials (% of times used in calls)																
	Printed material (% of times used in calls)					0,145											
	Very useful (% of calls)																
	Increase / Will begin to prescribe (% of calls)																
	Ln Avg number of products presented during the calls																
		Adjusted R^2	**0,995**	**0,975**	**0,528**	**0,527**	**0,774**	**0,270**	**0,802**	**0,483**	**0,842**	**0,975**	**-0,064**	**0,492**	**0,357**	**0,905**	**0,719**

Coefficient cells highlighted in light blue have sig. < 0,05, and cells with darker blue have sig. < 0,10.

As a subsequent step, we looked at the overall signals of the coefficients, seen below in table 10.92 (selecting the six core variables, most frequently referred in the theory).

Table 10.92 – Percentage of signals as expected – Model 8.4

		% signal as expected - Model 8.4				
		Market 1 - Blood	Market 2 - Pancreas	Market 3 - Heart	Market 4 - Liver	Global
Marketing expenditures flow	Ln Detailing flow	50,0%	75,0%	50,0%	80,0%	66,7%
	Ln Journal advertising flow	100,0%	75,0%	100,0%	60,0%	75,0%
	Ln Direct marketing flow	100,0%	0,0%	50,0%	0,0%	30,0%
Marketing expenditures stock	Ln Detailing stock	50,0%	75,0%	75,0%	60,0%	66,7%
Price	Ln Average drug price per DDD	100,0%	50,0%	75,0%	75,0%	71,4%
Drug age	Drug age	100,0%	100,0%	66,7%	20,0%	64,3%

Source: own elaboration

Globally, with the exception of Ln Direct marketing flow (mailing flow), the great majority of the products evidence a good percentage of signals as expected, based on previous theory.

Table 10.93 compares Model 8.4 against Model 7 (our best model applied to our data, among those developed by previous researchers). We conclude that, despite the issues revealed in table 10.91 above, we can accept Model 8.4 as adequate. Model 8.4 has a substantially higher percentage of signals as expected and sig. <0,05 than Model 7.

Table 10.93 – Comparison of Model 8.4 against Model 7 (signals as expected)

	Average elasticities		% signal as expected		% signal as expected and sig. <0.05	
	Model 7	Model 8.4	Model 7	Model 8.4	Model 7	Model 8.4
Ln Detailing flow	0,103	0,007	66,7%	66,7%	0,0%	20,0%
Ln Journal advertising flow	0,002	0,002	75,0%	75,0%	18,8%	16,7%
Ln Direct marketing flow	-0,001	-0,001	35,3%	30,0%	0,0%	0,0%
Ln Detailing stock	0,204	0,060	77,8%	66,7%	0,0%	26,7%
Ln Average drug price per DDD	-2,670	-6,150	64,7%	71,4%	0,0%	42,9%
Drug age	0,015	0,003	50,0%	64,3%	5,6%	50,0%
			61,6%	**62,3%**	**4,1%**	**26,0%**

Source: own elaboration

Despite the fact that Model 8.4 is not perfect and reveals several issues especially in the Reset test, we have evidence that it is acceptable, allowing us to continue our research.

10.6.4.3. Separate regressions for period 1 and period 2

The next step consisted of running separate regressions for Period 1 and Period 2 using SPSS, except for products LI4 and LI5, where we used Eviews. Below we present a series of tables summarizing the coefficients for all the eligible products in all four markets. Again, coefficient cells highlighted in light blue have sig. < 0,05, and cells highlighted with darker blue have sig. < 0,10. Table 10.94 summarizes the outputs of products in Market 1, table 10.95 in Market 2, table 10.96 in Market 3, and table 10.97 in Market 4.

Table 10.94 – Summary of the coefficients of Market 1 – Blood – Model 8.4 before and after detailing ceiling

			Product BL1			Product BL2		
			Period 1	Period 2	Global	Period 1	Period 2	Global
Constant			2,668	6,699	-2,507	5,941	12,265	6,454
Lagged sales	Ln Sales in DDDs lagged two periods					0,485	0,136	0,585
Marketing expenditures flow	Own	Ln Detailing flow	-0,059	0,175	-0,205	-0,073	0,080	0,063
		Ln Journal advertising flow	0,016	0,001	0,005	0,011	0,002	0,005
		Ln Direct marketing flow	0,019	-0,001	0,001	0,006	-0,001	0,002
	Competitive	Ln Competitive marketing expenditures flow	-0,025	-0,070	0,136			
Marketing expenditures stock	Own	Ln Detailing stock	0,645	0,187	0,165	0,028	0,013	-0,011
	Competitive	Ln Competitive global marketing expenditures stock	-0,114	0,058	0,631			
Price	Own	Ln Average drug price per DDD	0,177	-1,911	-0,642	-0,422	-2,093	-1,471
Drug age	Drug age		0,085	0,068	0,080	0,029	0,008	0,002
		Adjusted R^2	**0,981**	**0,996**	**0,995**	**0,967**	**0,756**	**0,975**

Source: own elaboration

Table 10.95 – Summary of the coefficients of Market 2 – Pancreas – Model 8.4 before and after detailing ceiling

			Product PA1			Product PA2			Product PA3			Product PA5		
			Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global
Constant			10,070	18,876	12,529	19,935	21,260	18,402	20,307	16,949	15,835	7,375	7,365	6,294
Lagged sales	Ln Sales in DDDs lagged one period					-0,287	-0,522	-0,360	-0,571	-0,464	-0,402			
Marketing expenditures flow	**Own**	Ln Detailing flow	0,031	0,088	0,032	-0,114	-0,045	0,002	-0,074	0,014	-0,027	0,057	0,064	0,058
		Ln Journal advertising flow	0,006	-0,003	0,000	0,002	0,007	0,003	0,002	0,002	0,002	-0,004	0,006	0,001
		Ln Direct marketing flow	-0,007	-0,002	-0,004	-0,002	0,000	-0,001	0,003	-0,006	-0,004	-0,002	-0,013	-0,006
Marketing expenditures stock	**Own**	Ln Detailing stock	0,423	0,013	0,195	0,050	0,002	0,076	0,110	0,334	0,214	0,021	-0,099	-0,049
	Competitive	Ln Competitive global marketing expenditures stock										0,440	0,329	0,406
Price	**Own**	Ln Average drug price per DDD	-0,502	-22,316	-0,897	-4,703	1,208	-0,637	-4,228	-0,336	1,475	-4,048	2,498	1,675
Drug age	Drug age		0,013	0,003	0,003	0,003	0,006	0,005	0,093	0,006	0,041	0,001	0,011	0,009
	Drug age squared								-0,001	-0,00003	-0,0003			
Additional variables	Printed material (% of times used in calls)					0,173	-0,216	0,145						
		Adjusted R^2	**0,522**	**0,396**	**0,528**	**0,221**	**0,517**	**0,535**	**0,617**	**0,576**	**0,774**	**-0,008**	**0,577**	**0,270**

Source: own elaboration

Table 10.96 – Summary of the coefficients of Market 3 – Heart – Model 8.4 before and after detailing ceiling

			Product HE1			Product HE2			Product HE3			Product HE4		
			Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global
Constant			-454,33	18,926	19,188	12,943	14,714	14,336	17,079	16,985	22,192	9,429	22,657	-0,817
Lagged sales	Ln Sales in DDDs lagged one period		-0,438	-0,515	-0,377							0,003	-0,173	0,518
	Ln Sales in DDDs lagged two periods											0,609	-0,102	0,487
Marketing expenditures flow	**Own**	Ln Detailing flow	0,054	-0,005	-0,001	0,031	0,040	0,024	-0,001	0,007	-0,011	0,040	-0,0004	0,025
		Ln Journal advertising flow				0,007	0,006	0,006						
		Ln Direct marketing flow				0,001	-0,005	-0,002	0,014	-0,003	0,014			
Marketing expenditures stock	**Own**	Ln Detailing stock	-0,010	0,077	0,099	0,031	-0,068	-0,082	0,001	0,186	0,053	0,038	-0,021	0,018
Price	**Own**	Ln Average drug price per DDD	-595,59	-2,868	1,048	-0,703	-0,203	-0,279	-0,456	-2,256	-1,769	-1,287	1,107	-0,268
	Competitors	Ln Average competitors drug price per DDD				-0,313	0,112	-0,348	0,791	-2,681	5,078			
Drug age	Drug age		0,009	0,006	0,015				-0,010	-0,050	-0,030	-0,035	-0,018	0,002
Additional variables	Ipad / Tablet (% of times used in calls)								0,104	0,162	0,198			
		Adjusted R^2	**0,404**	**0,618**	**0,802**	**0,193**	**0,187**	**0,483**	**-0,262**	**0,732**	**0,842**	**0,971**	**0,845**	**0,975**

Source: own elaboration

Table 10.97 – Summary of the coefficients of Market 4 – Liver – Model 8.4 before and after detailing ceiling

			LI1			LI2			LI3			LI4			LI5		
			Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global
Constant			11,42	16,513	16,977	27,542	23,893	26,458	11,389	13,613	12,752	-32,828	33,192	-38,519	7,829	11,654	12,010
Lagged sales	Ln Sales in DDDs lagged one period					-0,564	-0,618	-0,564									
	Ln Sales in DDDs lagged two periods					-0,428	-0,392	-0,350									
Marketing expenditures flow	**Own**	Ln Detailing flow	0,149	-0,041	-0,023	-0,021	0,012	0,010	0,034	0,020	0,019	-0,004	0,097	0,054	0,115	0,061	0,078
		Ln Journal advertising flow	0,010	0,0002	0,001	-0,002	-0,004	-0,001	0,007	0,008	0,008	0,001	0,002	-0,003	0,013	-0,001	0,003
		Ln Direct marketing flow	-0,001	-0,011	-0,005										-0,007	0,001	-0,007
	Competitive	Ln Competitive marketing expenditures flow															
Marketing expenditures stock	**Own**	Ln Detailing stock	0,199	-0,014	-0,112	-0,040	0,035	0,031	0,241	0,060	0,093	-0,149	-0,034	-0,010	0,391	0,164	0,221
		Ln Other marketing expenditures stock															
	Competitive	Ln Competitive global marketing expenditures stock													0,014	0,025	0,206
Price	**Own**	Ln Average drug price per DDD	-1,13	3,021	0,672	-1,443	3,786	-1,903	-0,991	-0,713	-1,826	-72,052	31,007	-78,24	-2,577	-3,421	-9,195
	Competitors	Ln Average competitors drug price per DDD				0,307	-0,024	0,232							0,275	0,532	1,222
Drug age	Drug age		0,003	0,006	-0,002	0,003	0,0004	-0,001	0,002	-0,004	-0,003	0,001	0,017	0,008	0,018	-0,029	-0,093
	Drug age squared																
Marketing expenditures interactions	Ln Drug price x Ln Detailing flow																
	Ln Drug price x Ln Detailing stock																
	Ln Drug price x drug age														0,048	0,056	0,173
		Adjusted R^2	**0,218**	**0,125**	**-0,064**	**0,093**	**0,207**	**0,492**	**0,370**	**0,141**	**0,357**	**0,809**	**0,820**	**0,905**	**0,830**	**-0,108**	**0,719**

Source: own elaboration

10.6.4.4. Coefficient interpretation examples

Table 10.98 below exemplifies how a series of variable coefficients (selected as an excerpt, representing all the independent variables types – logarithmized, non-logarithmizes, and percentage).

Table 10.98 – Coefficient interpretation example – Model 8.4

Independent variables (excerpt)	**Product**	**Coefficient** (reference: Model 8.4)	**Interpretation**
Ln Detailing flow	LI4	0,078	Each 1% increase in Detailing flow provokes a 0.078% increase in Drug sales, on average and ceteris paribus
Ln Detailing stock	PA3	0,214	Each 1% increase in Detailing stock provokes a 0.214% increase in Drug sales
Ln Average drug price per DDD	HE3	-1,769	Each 1% increase in Average drug price per DDD provokes a 1.769% reduction in Drug sales
Ln Average competitors drug price per DDD	HE3	5,078	Each 1% increase in Average competitors drug price per DDD provokes a 5.078% increase in Drug sales
Drug age	PA3	0,041	Each 1 month increase in Drug age provokes a 1.03% increase in drug sales, on average and ceteris paribus (considering the average drug age of 51.5 months for product PA3)
Drug age squared	PA3	-0,0003	
Ipad / Tablet (% of times used in calls)	HE3	0,198	Each 1% increase in the percentage of times Ipad / Tablet are used during the calls provokes 0.198% increase in Drug sales, on average and ceteris paribus

Source: own elaboration

10.6.4.5. Chow test

The next step was then to move to the Chow (1960) test. The computations were made in EXCEL, using the following formula:

$$\text{Chow} = \frac{(SSR_C - (SSR_1 + SSR_2) / k}{(SSR_1 + SSR_2) / (N_1 + N_2 - 2k)}$$

Where:

- SSR_C = Sum of square residuals of the combined regression (using the 48 observations)
- SSR_1 = Sum of square residuals of the regression before break (using the first 19 observations)
- SSR_2 = Sum of square residuals of the regression after break (using the last 29 observations)
- K = Number of independent variables including the constant
- N_1 = Number of observations before break (19 months)
- N_2 = Number of observations after the break (29 months)

To perform this test, we created table 10.99 and populated it with the data we extracted from the SPSS and Eviews outputs. The results are shown below:

Table 10.99 – Chow (1960) test using model 8.4

	Final model (8.4)														
	Market 1 - Blood		Market 2 - Pancreas				Market 3 - Heart				Market 4 - Liver				
	BL1	BL2	PA1	PA2	PA3	PA5	HE1	HE2	HE3	HE4	LI1	LI2	LI3	LI4	LI5
SSR_C	0,355	0,316	0,142	0,100	0,080	0,102	0,107	0,123	0,171	0,241	0,335	0,106	0,140	0,179	0,156
SSR_1	0,063	0,065	0,045	0,041	0,032	0,049	0,050	0,051	0,050	0,041	0,060	0,038	0,044	0,061	0,052
SSR_2	0,084	0,174	0,047	0,029	0,024	0,024	0,042	0,063	0,072	0,060	0,169	0,049	0,085	0,058	0,059
k	9	8	7	9	9	8	6	7	8	7	7	9	6	6	10
N_1	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
N_2	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29
Chow	4,7	1,3	2,6	1,4	1,4	1,6	1,0	0,4	1,6	6,7	2,2	0,7	0,5	3,0	1,1
Sig. F test	0,001	0,281	0,030	0,225	0,216	0,172	0,465	0,904	0,162	0,000	0,054	0,714	0,808	0,016	0,366

Having obtained the Chow result, we computed the p-value of the F test, using Excel. We used the Fdist(X;K;N_1+N_2-2K), where:

- X = output of the Chow (1960) test
- K = Number of independent variables including the constant
- N_1 = Number of observations before break (19 months)
- N_2 = Number of observations after the break (29 months)

Four of the products evidence a p-value lower than 0,05, signaling that the two distributions' coefficients (before and after the entry into force of the detailing ceiling) are different.

However, we do have many variables that cumulatively impact the dependent variable (Ln Drug sales in DDDs). Our goal is to conclude whether the coefficients of our most important variable of interest – Ln Detailing flow (calls) – changed, to signal a change in prescription behavior. To do this, we ran additional regressions using the exact individual Model 8.4 equations for each product, performing the following steps:

- **Step 1)** We ran a regression with Ln Detailing flow (calls) as dependent variable and all the rest of variables of Model 8.4 as independent variables, using the 48 months of observations. We activated the option to save the unstandardized residuals. The idea is to capture the part of the unique contribution provided by Ln Detailing flow (calls) that is not explained by the other independent variables

- **Step 2)** We ran three regression models (one with the full time series, one with Period 1, and one with Period 2) using Ln Drug sales in DDDs as dependent variable and the unstandardized residuals from Step 1 as the unique independent variable, excluding the constant in SPSS options. The coefficient obtained for the whole dataset (full time series with 48 observations) was exactly the same as the one obtained in the normal regression with the full Model 8.4 for the variable Ln Detailing flow (calls) using the same 48 observations

- **Step 3)** We ran the Chow (1960) test again, with the outputs obtained from step 2

The goal of applying this procedure was to investigate eventual structural breaks motivated by the entry into force of the detailing ceiling, isolatedly in Ln Detailing flow (calls). Table 10.100 below summarizes the findings.

Table 10.100 – Chow (1960) test using model 8.4 – Isolated impact of Ln Detailing flow (calls)

	Final model (8.4)														
	Market 1 - Blood		Market 2 - Pancreas				Market 3 - Heart				Market 4 - Liver				
	BL1	BL2	PA1	PA2	PA3	PA5	HE1	HE2	HE3	HE4	LI1	LI2	LI3	LI4	LI5
SSR_C	6480,5	8050,1	9746,6	9677,0	8953,9	8198,3	10382,5	10116,8	6715,0	10039,8	11240,4	8503,8	9602,7	8998,7	6624,8
SSR_1	1930,0	2888,5	3802,7	3700,6	3489,8	3235,2	3790,3	3894,2	4187,8	4246,2	4330,9	3378,3	3816,4	3444,3	2618,4
SSR_2	4506,5	5141,3	5882,6	5832,0	5443,5	4959,5	6255,9	6082,5	2418,1	5770,8	6746,0	5107,9	5785,9	5526,6	3996,3
k	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
N_1	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
N_2	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29
Chow	0,314	0,117	0,291	0,697	0,106	0,020	1,540	0,646	0,760	0,105	0,679	0,095	0,002	0,142	0,070
Sig. F test	0,578	0,734	0,592	0,408	0,746	0,887	0,221	0,426	0,388	0,747	0,414	0,759	0,965	0,708	0,793

The F-test compares two R^2:

- H_0: $R^2_1 = R^2_2$
- H_a: $R^2_1 \neq R^2_2$

Our findings are clear: since no Sig. F test was lower than 0,05, or by other words we did not reject the null hypothesis in any product, none of the products evidenced a structural break in the effect of our specific variable of interest (Ln Detailing flow (calls)), using August 2013 as a reference. These results demonstrate that - with the reserve of the misspecification as seen in the Reset test for a substantial percentage of products – there is no evidence that the Detailing flow elasticities are statistically different from Period 1 to in Period 2. Having in mind this irrefutable fact, we decided to nevertheless develop a group of tables (10.101 and 10.102) in order to help us gain additional insights and search for patterns in our results so far, for purely intellectual curiosity. The goal was to evaluate the extent to which our results show differentiated changes in detailing elasticities between products, according to their detailing intensities – analyzes that - if the Chow (1960) tested had produced significant results – would contribute to Liu et al (2016) research.

Table 10.101 – Average elasticities in Period 1, Period 2 and Global – Model 8.4

	Blood			Pancreas			Heart			Liver		
	Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global	Period 1	Period 2	Global
Average Detailing elasticity	-0,066	0,128	-0,071	-0,025	0,030	0,016	0,031	0,010	0,009	0,055	0,030	0,028

This aggregate view does not provide sufficient detail. Therefore we created two additional tables.

Table 10.102 – Average elasticities of highest and lowest detailing intensity – Model 8.4

			Average Detailing elasticity			Results aligned with Liu, Gupta, Venkataraman & Liu (2016) prediction?
			Period 1	Period 2	Global	
Market 1 - Blood	Drug(s) with the highest detailing intensity	BL1	-0,059	0,175	-0,205	No
	Drug(s) with the lowest detailing intensity	BL2	-0,073	0,080	0,063	Yes
Market 2 - Pancreas	Drug(s) with the highest detailing intensity	PA2	-0,114	-0,045	0,002	No
	Drug(s) with the lowest detailing intensity	PA1	0,031	0,088	0,032	Yes
		PA5	0,057	0,064	0,058	Yes
Market 3 - Heart	Drug(s) with the highest detailing intensity	HE2	0,031	0,040	0,024	No
	Drug(s) with the lowest detailing intensity	HE3	-0,001	0,007	-0,011	Yes
		HE4	0,040	-0,0004	0,025	No
Market 4 - Liver	Drug(s) with the highest detailing intensity	LI4	-0,004	0,097	0,054	No
		LI1	0,149	-0,041	-0,023	Yes
	Drug(s) with the lowest detailing intensity	LI2	-0,021	0,012	0,01	Yes
		LI3	0,034	0,020	0,019	No

Source: own elaboration

Table 10.102 above evidences the average detailing elasticities of products with the highest and lowest detailing intensity, in each market. In some markets, due to the proximity in detailing intensity, we chose two products. Liu et al (2016) suggested that drug sales

(measured in market share) may have differentiated impacts from a detailing ceiling, depending on their detailing intensity. Table 10.103 evidences the percentage of cases where results are aligned with Liu et al (2016) counterfactual simulations.

Table 10.103 – Percentage of cases where results adhere to Liu et al (2016) predictions

% of cases where (from Period 1 to Period 2)…	
Drug(s) with the highest detailing intensity evidenced a reduction in Detailing elasticity	Drug(s) with the lowest detailing intensity evidenced an increase in Detailing elasticity
20,0%	71,4%

Source: own elaboration

Our results suggest that drugs with the lowest detailing intensity (71,4% of the eligible cases, or five out of seven products) will see their detailing elasticities increased after a detailing ceiling. Again, these conclusions are however totally limited by the fact that the Chow (1960) test produced non-significant results for all the products in analysis. **This is one of the main evidences obtained in our thesis, to help us answer our research question.**

10.7. Conclusions

We divided the conclusions in three subchapters: Models 1 to 6, Model 7, and Model 8.4 (our final model).

10.7.1. Models 1 to 6

In **Model 1 (Wittink, 2002 – simplified),** detailing flow is the most impactful promotion instrument in terms of prescription behavior, for three of the four markets. Mailing flow and Journal advertising have positive global average elasticities, but of relatively low magnitude comparing to previous results from Leeflang & Wieringa (2010). Non-promotional variables evidenced however a much higher impact on prescription behavior than detailing: Public reimbursement (Market 1 only) resulted in a very influencial variable with an average elasticity of 1,995, and Loss of exclusivity (Market 3 only) had an average elasticity of -0,062.

In **Model 2 (Wittink, 2002 – complete),** detailing flow evidences global higher elasticities than Model 1, especially in the case of Market 1 (Blood), where the average elasticity is 0,084 for the three products, and 0,287 for product 1 (the one with the elasticity signal as expected). However, and very curiously, Mailing and Journal advertising flows evidence higher average elasticities than detailing flow. Again, Public reimbursement (Market 1 only) is the most impactful variable to explain variations in sales in DDD (our dependent variable), followed by Loss of exclusivity (Market 3 only).

In **Model 3 (Rizzo, 1999)** the average elasticity of Detailing flow reached 0,087, a value much higher than the one obtained in Models 1 and 2. Also, detailing stock elasticity obtained a very high elasticity (average of 0,146 for the 18 products). Such as in Models 1 and 2, Public reimbursement (Market 1 only) is the most impactful variable to explain variations in sales in DDD (our dependent variable), followed by Loss of exclusivity (Market 3 only).

In **Model 4 (Windmeijer et al, 2006)** we obtained a higher number of coefficients as expected, comparing the results against the previous models (Sales in DDDs lagged two periods, Global marketing expenditures flow, Global marketing expenditures stock, Average drug price per DDD, Drug age, Drug age squared, Global marketing expenditures flow x Ln Average drug price per DDD, Public reimbursement, and Loss of exclusivity, all with more than 50% of the products' elasticities with signal as expected. Ln Global marketing expenditures flow average coefficient reached 0,035, and Global marketing expenditures stock average coefficient was 0,247. Five products (BL1, HE4, HE5, LI4 and LI5) evidenced seven variables with the signal as expected, from a maximum of 11 main variables.

In **Model 5 (an adaptation of Model 4, with non-aggregated marketing investments)** the average detailing elasticities reached 0,149, a much higher value than in previous models. Journal advertising and Direct marketing (mailing) lows evidenced almost zero elasticity, but detailing stock obtained a relatively high elasticity (an average of 0,271 for the 18 products).

In **Model 6 (an adaptation of Model 4, with new variables that help characterize the detailing initiatives)**, global marketing expenditures flow average elasticity reached 0,029, and Global marketing expenditures stock average elasticity reached 0,153. Average price elasticity reached -1.631, meaning that for each percentage point price increase in drug sales, sales in DDDs drop 1,631 per cent.

10.7.2. Model 7

Detailing flow - the most impactful promotion instrument - evidences a relatively small elasticity (average of 0,103 for the 18 products), reduces the price elasticity of drugs, especially in the case of younger drugs, shows carry-over effects, and is most impactful during the initial stages of product life cycle. Detailing stock is particularly stronger in the case of younger or much younger products. In eight out of 18 products competitive detailing negatively impacted own product sales.

Journal advertising and direct marketing (mailing) flows showed almost null elasticities in our data, suggesting a low impact on physician prescription behavior measured with drug sales. Drug price has a very strong effect on drug sales, with an average elasticity of -2,67 for the 18 products. Model 7 results suggest a powerful impact of policy changes in drug sales, seen in the positive effect of public reimbursement (Market 1 - Blood) and negative effect of loss of exclusivity (Market 3 - Heart).

The usage of iPad / Tablets and printed materials during the calls show a positive coefficient in its ability to impact drug sales. There appears also to be a positive relation between drug sales and the percentage of physicians that declares he or she will increase his or her prescription of the detailed drug brand. Results also suggest that the higher the number of additional drugs presented during a call, the lower will the sales of the promoted drug be (average elasticity of -0,034, however non-significant results at sig. = 0,05).

10.7.3. Model 8.4

We focus the conclusions of Model 8.4 in the part related to the detailing ceiling and Chow (1960) test. In our data, the effect of Order 8213-B/2013 (that imposed a detailing ceiling) on prescription behavior measured through detailing elasticities was not significant. Not one single product evidence significant changes in its elasticities, before and after the entry into force of this ceiling (measured with a Chow (1960) test). Despite the fact that the elasticities are not significantly different from one period to another, there were some interesting patterns observed: 71,4% of the drugs with the lowest detailing intensity evidenced an increase in detailing elasticity (or the ability of detailing to more intensely impact drug sales measured in DDDs).

10.8. Discussion

In order to provide additional detail, we separate the discussion in the case of Models 1 to 6, Model 7 and Model 8.4.

10.8.1. Models 1 to 6

Model 1 (Wittink, 2002 – simplified) results are globally aligned with the ones obtained by Leeflang & Wieringa (2010). Detailing flow elasticity is generally positive – but very small. Competitive marketing expenditures flow resulted in a positive average elasticity, such as the one obtained by Leeflang & Wieringa (2010). This result seems counterintuitive, and an explanation may be the fact that, by developing marketing initiatives, competitors end up stimulating the sales of the market as a whole. Drug price elasticity resulted in a negative average value of -0.172, as predicted by the theory. In the same wavelength, drug age (positive average coefficient) and drug age squared (negative average coefficient) produced results very close to the ones reached by Leeflang & Wieringa (2010). Globally, the average elasticities are reasonably close to the ones reached by Leeflang & Wieringa (2010).

Model 2 (Wittink, 2002 – complete) evidences results globally aligned with what the theory suggests in terms of expected signal, especially in the case of detailing, Competitive direct marketing flow, Drug age, Drug age squared and Public reimbursement (all with more than 50% of the products' elasticities with signal as expected). However, the main promotion instruments average elasticities magnitudes are lower than what it would be expected, especially in the case of detailing, reaching an average (for the 18 products) of 0,02 (against an expected elasticity higher than 0,3, as found by Kremer et al (2008)).

Model 3 (Rizzo, 1999) global results also observe, reasonably, the expected coefficient signals, especially regarding Detailing flow, Detailing stock, Drug age, Drug age squared, the interaction variable Average Drug price x Detailing flow, Public reimbursement and Loss of exclusivity, all with more than 50% of the products' elasticities with signal as expected. In this model the average elasticity of Detailing flow reached a value much higher than the one obtained in Models 1 and 2, but still substantially distant from the typical, expected average elasticities such as the ones found by Kremer et al (2008). More interestingly, Detailing stock average elasticity is much higher than the one obtained in Detailing flow, as demonstrated by Kremer et al (2008). Regarding the interaction variable Average drug price x Ln Detailing

flow, only six products (three of which in Market 3 (Heart) had a signal as expected. In this case, the effect of detailing flow lowers the price elasticity of demand.

Model 4 (Windmeijer et al, 2006) appears to globally observe the expected coefficients signals too. Global marketing expenditures flow average coefficient reached 0,035, and Global marketing expenditures stock average coefficient was 0,247, substantially higher than the ones obtained by Leeflang & Wieringa (2010), but noticeably lower than the ones predicted by Kremer et al (2008).

Model 5 is, as seen before, an adaptation of Model 4, the main difference being the inclusion of non-aggregated marketing investments, in addition to additional interaction variables. Therefore, the comparison against a specific model is not directly possible. However, we can analyze the model results globally, concluding that it generally produces results as expected by the theory (globally, 11 out of 19 variables reveal at least 50% coefficient signals as expected by the theory).

Model 6 consists of Model 4 with the inclusion of new variables that help characterize the detailing initiatives. In terms of comparison of Model 6 results against theory, it is quite close to the results of Model 4.

10.8.2. Model 7

We now analyze results from Model 7 in light of previous theory. Detailing flow has on average a positive, but modest effect on brand sales, which is consistent with previous research conducted by Kremer et al (2008), Stremersch & Van Dyck (2009), and Stremersch & Lemmens (2009). It also appears to be the promotion instrument that generates a higher effect on prescription behavior, in line with research performed by Pitt & Nel (1988), Narayanan, Desiraju & Chintagunta (2004), Narayanan, Manchanda & Chintagunta (2005), Kremer et al (2008), and Dave & Saffer (2012), to name a few. Detailing also appears to reduce price elasticity of drugs (reduces physicians' price sensitivy) as predicted by Rizzo (1999), Gönül et al (2001), Narayanan et al (2004), and Windmeijer et al (2006). In our case, this is especially evident in the case of much younger (quartile 1) and much older (quartile 3) products. Our data also suggest that detailing evidences carry-over effects, that is, the cumulative investment of detailing has a positive effect on drug sales, as demonstrated previously by Narayanan et al (2004), Zoltners, Sinha & Lorimer (2004), Yi (2008), Montoya, Netzer & Jedidi (2010), and Liu et al (2016). In our data, the effect of detailing stock is especially strong among younger or much younger products. The theory, including Dong,

Manchanda & Chintagunta (2009) and Liu et al (2016), predicts that detailing efforts performed by competitor drug brands (competitive detailing) affect own brand number of prescriptions. In our data, this was partially seen, since it only was verified in eight out of 18 products. Our data suggests that detailing efforts appear to have a higher effect on prescriptions at the initial stages of the product life cycle. This evidence is supported by previous research conducted by Narayanan et al (2003), Manchanda, Rossi & Chintagunta (2004), Manchanda & Honka (2005), Narayanan et al (2005), and Dave (2013).

Detailing elasticities vary between therapeutic classes, in line Kremer et al (2008) and Stremersch & Van Dyck (2009). Average detailing elasticities from our Model 7 are substantially lower than the one expected by Kremer et al (2008). In the case of detailing flow, the average elasticities are approximately two thirds lower.

Our results are also in line with previous research in the field of changes in pharmaceutical policy. This is seen in the case of public reimbursement, positively impacting drug sales as suggested by Scherer (1993), in our case seen in two of the three products in Market 1 (Blood). The theory also suggests that loss of exclusivity negatively impacts drug sales (Aitken et al, 2013), which was also verified in our results for the two eligible products in Market 3 (Heart).

10.8.3. Model 8.4

With model 8.4 we obtained what we believe may be a more calibrated and adapted model to the specificities of our research. If by the one hand Model 8.4 produced elasticity magnitudes substantially lower than the ones suggested by previous work such as Kremer et al (2008) and Leeflang & Wieringa (2008), by the other hand the percentage of signals as expected and significant (sig. < 0,05) is substantially higher than than in previous research from Leeflang & Wieringa (2008).

As seen during the analysis of the structural breaks in detailing flow elasticity, our results – contrary to what is suggested by the theory on pharmaceutical marketing (Liu et al (2016), Larkin, Ang, Avorn & Kesselheim, 2014; Larkin et al, 2017) - did not provide sufficient evidence to say that detailing elasticities were significantly different before and after the entry into force of the 2013 detailing ceiling. This conclusion is robustly backed by the fact that all 15 eligible products in our analysis evidenced the same result: no significant differences in detailing flow elasticities from period 1 to period 2. We were intrigued by these unexpected findings, which demanded further research to identify the potential explanations for this

behavior in Portugal. The qualitative phase, as described before, consisted of non-structured interviews (at the beginning of our research) and in-depth interviews (at a later phase).

When analyzing detailing elasticities before and after the entry into force of the detailing ceiling in light of products with higher and lower detailing intensity, we found that 20% of the drugs with the highests detailing intensity evidenced a reduction in detailing elasticity, and 71,4% of the drugs with the lowest detailing intensity evidenced an increase in detailing elasticity, which only tangentially observes previous findings from Liu et al (2016), given that these results from our research were not statistically significant.

10.9. Contribution to the theory

We describe the contribution to the theory separating Models 7 and 8.4, for a better organization. The reasons for this speration are two: by the one hand, Model 7 is closest to previous research in terms of the variables used to study detailing and pharmaceutical marketing, thus providing a better comparison against prior estimates on elasticities; by the other hand, Model 8.4 (our final model) had to be substantially adapted by removing a series of variables, given the break tests we had to perform.

10.9.1. Model 7

Our research with Model 7 includes several new contributions to the theory which, to the extent of our knowledge, have not previously been addressed. The first is the evidence that detailing appears to reduce price elasticity especially of much younger and much older drugs. A possible explanation, **to be verified by further research**, may be, for the first case, the higher receptiveness of doctors when receiving PSRs promoting more recent drugs and their natural willingness to test them; in the second case, may be explained by the cumulative capital of the relational building generated after years of loyal visits (previously described when addressing reciprocity). Our research also demonstrates that the carry-over effects appear to be much higher for more recent drugs. A possible explanation may be the fact that doctors may – again – be more receptive to initiate or reinforce prescription of drugs launched more recently in the market.

The new variables used in our research also allowed us to generate new insights in the field of detailing. The first one is the apparent evidence that the use of tablets (such as iPads or equivalent devices) during the calls have, on average, a positive effect on drug sales, especially in the case of older drugs. One possible reason for this global positive effect may

be the relatively novelty effect of this type of call in Portugal, resulting in a higher attention from doctors (the time series started in January 2012 and at that time iPads were not that common in the market). In the case of older drugs, this effect may be even higher, given that for years PSRs most likely did not use such devices, during the initial phases of the products life cycle. The second one is the evidence that laptop-based materials appear to have an average negative effect on drug sales, but a positive effect on older drugs. Again, this may be explained by the fact that older drugs were mainly promoted, for years, using printed materials. Our results also seem to suggest that the use of printed materials during the calls does not provoke a substantial impact on drug sales. One potential explanation may reside on the fact that delivering printed materials may no longer translate into a competitive advantage of the companies in relation to their competitors. Another contribution is the apparent suggestion that a higher declared intention (by doctors) of starting prescribing or increasing prescriptions of the detailed product to be positively associated with drug sales, but only for older products. This may be explained, as addressed above, by the sense of loyalty or reciprocity, rewarding PSRs that have been visiting them for longer (promoting drugs launched in the market many years before). Finally, another interesting contribution is the seeming conclusion that a higher average number of products presented during the calls negatively impacts drug sales of the product analyzed. This may be explained by the dilution of the message of the main product when other products are promoted during the call (doctors awareness of the message of the main product may be therefore lower, which may have a negative effect on his or her prescription of the main product).

From a theoretical point of view, the new variables addressed above brought novel, fresh data to the study of pharmaceutical marketing and specifically detailing, as demonstrated by the deep analysis of the models, variables and conclusions of more than 40 quantitative papers in pharmaceutical marketing involving detailing. These variables are new, launched by IMS Health in the second decade of 2000, therefore with little time for analysis by previous researchers.

10.9.2. Model 8.4

Our research with Model 8.4 also includes new contributions to the theory on pharmaceutical marketing and marketing regulation policy. The main contribution is the evidence that the entry into force of a detailing ceiling may not directly lead to a significant change in physician prescription behavior (and therefore a significant effect on drug sales). This was clearly seen on all the products we analyzed with separate regression models and series break test (Chow,

1960). Another contribution – consequence of the previous one – is the evidence that, from a pure statistical point of view, drugs with higher and lower detailing intensity do not always suffer differentiated impacts after the entry into force of a detailing ceiling. Our research demonstrated that seven out of 10 drugs with a previous lower detailing intensity saw their detailing elasticities grow, but this effect was not statistically significant.

10.10. Limitations

Our research incorporated a series of limitations, which we tried to summarize in the subchapters below. For a better interpretation, we separated the limitations to Model 7 and to Model 8.4.

10.10.1. Model 7

We start with a data procedure limitation (common to all models, including Model 8.4). For detailing stock calculation (starting from January 2012), detailing flow for the period of January 2011 to December 2011 may not fully represent the real investments made by manufacturers, since it was calculated using Rizzo (1999)'s and Windmeijer et al (2006) approaches. This limitation would only be fully solved by having access to more data, which was not possible given the specificities of IQVIA's database (no monthly information available for promotional investments before January 2012). However, we believe the procedures observed are reliable and provided sufficient robustness for our detailing stock variable.

Another limitation resides in the fact that the contribution to the theory allowed by Model 7, despite its global adherence to previous research conducted by many scholars investigating pharmaceutical marketing and detailing (especially in terms of the expected signals of the coefficients), is based mostly in non-significant coefficients, which limit the inference of our results. However, the percentage of coefficients that simultaneously have the expected signal and are significant is in line of Leeflang & Wieringa (2010).

Another limitation is related to this previous one. Our option was to directly apply several models developed by other researchers in the past, and test the extent to which they would be adequate to our data. This decision – despite resulting in many non-significant independent variables coefficients, had to be made in order to compare our results against the outputs of the several models, allowing us to critically discuss the results in light of theory. We tried to overcome this limitation by applying Model 7 and step by step manually remove the non-

significant variables, which we called Model 8.1. However, the results obtained in a sample of 10 products demonstrated that almost all variables ended up removed from Model 8.1, suggesting that there is a very high degree of heterogeneity. We also did not test the robustness of models 1 to 8.3 in terms of collinearity, normality of residuals, homoscedasticity, and reset test, only performing it in Model 8.4, our final model, used to perform the Chow (1960) test.

An additional limitation resides in the fact that we used, for promotion expenditures, data coming from a panel comprising a sample of physicians, whereas sales data almost perfectly represents the population. However, IQVIA guarantees sample representativeness in terms of specialties, regions and doctor characteristics, and therefore we assumed panel full representativeness for inference purposes. Such data from IQVIA was also used, as noted before, by a great number of researchers studying time series of drug sales and pharmaceutical promotion expenditures. By other words, the inferencial part is conditional to the assumption of the correct representativeness of IQVIA doctor panel.

10.10.2. Model 8.4 and Chow test

The model we used to run the Chow (1960) test suffered from severe misspecification (60% of products with p-values lower than 1%, and 73,3% with p-values lower than 5% in the Reset). This is the equivalent to say that our model lacks non-linear variables or interactions we were not able to capture, in line of the conclusions reached by Wieringa & Leeflang (2013) in their application of pharmaceutical marketing models. However, despite this important limitation, Model 8.4 was sufficiently robust to allow us to perform the analyses (seen in the percentage of product coefficients with signal as expected and statistically signiticant at 0,05).

11. Empirical study - qualitative

This chapter starts by exploring the fieldwork procedures and development, and then moves to the content analysis of the collected data.

11.1. Fieldwork

This sub-chapter is divided in two components: the non-structured interviews that took place at the beginning of the PhD thesis development, and the in-depth interviews made with a group of pharmaceutical industry stakeholders.

11.1.1. Non-structured interviews

These interviews occurred in December 2016, April 2017 and May 2017, and were made with pharmaceutical industry high officers to understand several aspects:

- The main issues pharmaceutical companies face at the moment
- Main communication channels and promotion instruments used by the pharmaceutical companies to interact with physicians
- Implementation of the detailing ceiling in 2013
- Existence of previous detailing ceilings before 2013

The meetings took place in informal settings, and sound was not recorded. Manual notes were taken, written at the researcher's physical notebook, and later written in digital format.

The characterization of the interviewees is summarized below, in table 11.1.

Table 11.1 – Characterization of the participants in the non-structured interviews

Interviewee	Gender	Age interval	Professional affiliation	Years of professional experience
1	M	45 to 54	IQVIA	>20
2	M	45 to 64	IQVIA	>20
3	M	>64	Top pharmaceutical company	>20
4	M	35 to 44	MSD	10 to 15

Source: own elaboration

11.1.2. In-depth interviews

As described before, we selected a list of 15 high officers to interview. The next sub-chapters will describe the procedures, difficulties, and alternatives developed during this phase.

11.1.2.1. Initial procedures

We used our personal and professional network to find officers that matched the defined profiles. We used face-to-face, phone, and digital communication interactions in order to find and invite a first series of officers. The contacts started at the last two weeks of December 2018, scheduling the first interviews for January the 4th 2019.

11.1.2.2. Difficulties

A first constraint was derived by the fact that the researcher was developing his professional activity in Barcelona, every Monday to Thursday, which significantly limited the window of opportunity to meet in Portugal (Fridays only). Then after a very strong first wave of interviews, we started facing difficulties to obtain more relevant profiles and their acceptance of the interviews. The main constrain was their availability to meet. For instance, only at the third attempt, and after more than 10 e-mail and phone messages, we were able to interview a very high officer from a top pharmaceutical company. In order to overcome this difficulty, we reached a reference consultant in the pharmaceutical industry (one of the interviewees), whom we have a very close professional relation with, to assist us with relevant profiles. Several names were then suggested, which we contacted, resulting in a few more interviews. This was also the officer who allowed us to reach a very high officer from the 21st Constitutional Government' Ministry of Health (which, following his recommendation, we reached at a social network, and surprinsigly answered us).

We faced another difficulty, when we contacted Infarmed CIMI (Centro de Informação do Medicamento e Produtos de Saúde, or Medicine and health products center of information). We first received a request to send the script, which we did, and a few days after we received a phone call, arguing that Infarmed cannot provide us with the requested information. We recorded our feedback after this call, which we transcribe now: "Today is the 20th of December 2018. I recently received a telephone call from Infarmed, by the person ------, who told me that Infarmed can not help me to answer the qualitative guide, because it is not part of the Infarmed roles to help in this scope, in doctoral thesis, in particular in the interpretation or commentary on the measures that have been taken in the field of health". Given the impossibility to have Infarmed's contribution, we decided to remove it from the list of institutions in our eligible profiles.

Another difficulty we faced was also unexpected. We thought the less difficult target to reach would be the pharmaceutical sales representatives (reps), given that we have a relevant network among these professionals. However, to our astonishment, this was the most difficult

target to reach, and the main reason is simple: most pharmaceutical companies, through their legal and compliance departments, asked their PSRs to sign confidentiality and non-disclosure contractual terms, which prohibit them to speak about their professional activity. We even suggested reps to submit the transcriptions of their eventual interviews to their compliance officers, but that proposal was not accepted.

The way we solved these issues consisted of three activities: the first was to ask a doctor we interviewed to provide us with a list of PSRs in the markets of interest (Blood, Pancreas, Heart, and Liver). To our amazement, after the interview, the doctor pulled his phone and contacted two PSRs, who immediately acceded to be interviewed (one of which cancelled the meeting a few hours before the scheduled time); the second was to ask contacts to a former colleague who we worked with at Cegedim and to a former client who we provided consulting services to, which resulted in two additional interviews with PSRs; and the third was to ask assistance to a reference operations director, whose professional network allowed us to interview two additional PSRs.

The final difficulty was the inability to reach high officers from the 19th Constitutional Government' Ministry of Health. We identified three relevant profiles, reached them directly through social networks, and indirectly through contacts from our personal and professional network, but were not able to have a reply. These would surely be very interesting profiles to interview, but we believe this could partially be substituted by a deep analysis of the preamble of Order 8213-B/2013. Following the procedures prescribed in the study protocol, we opted to make some telephone interviews, on the second half of the fieldwork phase, in order to complete all profiles.

11.1.2.3. Adaptations to the list of profiles to interview

During the fieldwork, we added additional profiles to our list of officers, in order to both overcome the difficulties described in the previous sub-chapter, and to increase the robustness of our data collection, expanding the geographic scope to other areas than the Greater Lisbon (including South – Algarve and Alentejo, Greater Oporto, and Center). Also, one of our contingency plan PSRs accepted being interviewed. The goal was to increase the likelihood of finding regional patterns in the answers of the interviewees, and therefore increase the representativeness and robustness of this data collection step and content analysis. As a result, we ended up with five more interviews than planned (20 completed versus 15 estimated).

Therefore, the final list of interviewed officers is shown below, in table 11.2.

Table 11.2 – Final list of interviewed officers – in-depth interviews

Scope	Int.	Position and Institution	Region	Date	Channel	Duration (HH:MM:SS)	Gender	Age interval	Academic qualif.	Years of experience
Government / Tutelage		Infarmed officer	Greater Lisbon	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		High Officer from the XIXth Ministry of Health	Greater Lisbon	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	I1	High Officer from the XXIst Ministry of Health	Greater Lisbon	11-ene	Face to face	0:35:09	M	≥45	PhD	>20
Health Care Organizations	I2	NHS ACES Functional Unit Coordinator	Greater Lisbon	04-ene	Face to face	0:55:38	F	≥45	Degree	>20
	I3	NHS Hospital Clinical Director	Greater Lisbon	11-ene	Face to face	0:54:16	F	≥45	MSc / MBA	>20
Health Care Providers	I4	NHS + Private Practice General Practitioner (physician)	Greater Lisbon	16-feb	Face to face	0:44:22	M	≥45	Degree	>20
	I5	NHS + Private Practice General Practitioner (physician)	Center	19-ene	Face to face	0:50:08	M	≥45	Degree	>20
	I6	NHS + Private Practice General Practitioner (physician)	Greater Oporto	16-feb	Telephone	0:36:21	F	≥45	Degree	>20
	I7	NHS + Private Practice General Practitioner (physician)	Algarve / Alentejo	11-mar	Telephone	0:38:37	M	≥45	Degree	>20
	I8	NHS + Private Practice Hospital Specialist (physician)	Greater Oporto	22-feb	Telephone	0:45:54	F	≥45	Degree	>20
Pharmaceutical Industry officers	I9	High Officer from a top pharmaceutical company	Greater Lisbon	25-ene	Face to face	0:28:37	F	≥45	Degree	>20
	I10	High Officer from a top pharmaceutical company	Greater Lisbon	25-ene	Face to face	0:55:36	M	≥45	Degree	>20
	I11	High Officer from APIFARMA	Greater Lisbon	01-feb	Face to face	1:19:53	M	≥45	Degree	>20
	I12	High Officer from APIFARMA	Greater Lisbon	01-feb	Face to face	1:19:53	M	≥45	PhD	>20
Pharmaceutical Sales Representatives	I13	Rep Market 1 - Blood	Algarve / Alentejo	09-mar	Telephone	0:46:49	M	≥45	Degree	>20
	I14	Rep Market 3 - Heart	Greater Lisbon	22-feb	Face to face	1:04:48	M	≥45	Degree	>20
	I15	Rep Market 2 - Pancreas	Algarve / Alentejo	06-mar	Telephone	0:42:20	M	≥45	Degree	>20
	I16	Rep Market 2 - Pancreas	Greater Lisbon	11-mar	Telephone	0:53:41	F	≥45	Degree	>20
	I17	Rep Market 4 - Liver	Greater Oporto	06-mar	Telephone	0:45:06	F	≥45	Degree	>20
Pharmaceutical industry consultants	I18	High Officer from IQVIA	Greater Lisbon	04-ene	Face to face	0:40:50	M	≥45	MSc / MBA	>20
	I19	High Officer from Lean Health Consulting	Greater Lisbon	15-feb	Face to face	0:41:46	M	≥45	MSc / MBA	>20
	I20	High Officer from hmR	Greater Lisbon	04-ene	Face to face	0:53:47	M	≥45	MSc / MBA	>20
					Avg	**0:49:41**				

In the table above, we did not provide a higher detail on the age interval and years of experience in order to mitigate the possibility of identification of the participants.

11.1.2.4. Sound recording, notes and researcher feedback

All interviewees gave their consent to record the interview. For that, we used a smartphone with the app "REC Voice Recorder", which generated MPEG-4 Audio files, then saved in the researcher's laptop. The interviews duration ranged from (HH:MM:SS) 00:28:37 to 01:19:53, with an average of 00:49:41, globally inside the 45 to 60 minutes interval that was announced at the beginning of each interview.

The researcher took hand-written notes whenever relevant, to gather impactful insights whenever they appeared. Finally, the researcher recorded his own feedback speech after each interview, at the same app, producing sound files with duration of between 1 and 10 minutes.

11.1.2.5. Evolution of the number of in-depth interviews

In nine of the 11 weeks between the beginning of January 2019 and the middle of March, there were in-depth interviews performed, whose evolution is shown below in figure 11.1 (performed interviews and cumulative interviews in each week).

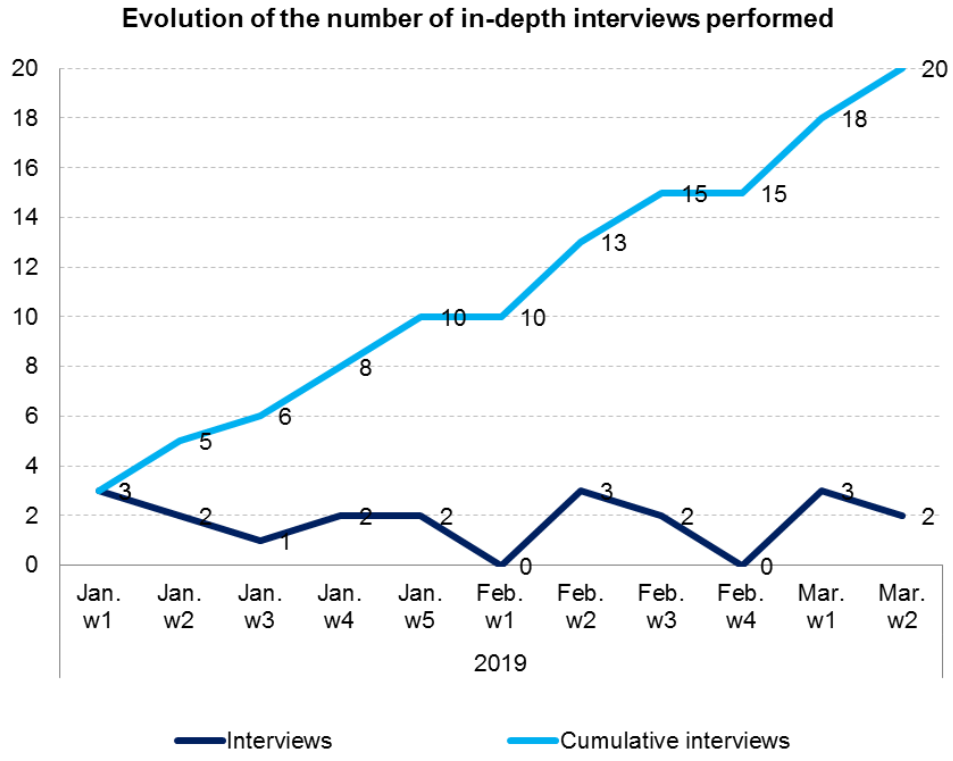


Figure 11.1 – Evolution of the number of in-depth interviews (performed + cumulative)

11.2. Transcriptions

The transcriptions of the face-to-face in-depth interviews were assisted by NVivo Transcription software. The quality of the automatic transcriptions may be considered reasonable, but it seems to be more calibrated to Brazilian Portuguese than to European Portuguese. Moreover, the automatic transcription did not use punctuation. All automatic transcriptions were adequately validated, to amend imprecisions and to include pontuation. Overall, despite these limitations, it helped reduce the transcription time by around 30%, according to our perception. The interviews made by telephone, given the pooerer quality when compared to the face-to-face ones, were not able to be automatically transcribed (the software did not appear to separate the natural background noise from human speech). Normal, fully manual transcriptions were made in these cases (seven out of 20 interviews).

To the extent possible, we removed all references to names, pharmaceutical companies, and comments from interviewees that could nominatively identify them as participants or expose their companies or other companies. Therefore, the interviewees appear as I1 (interviewee 1), I2 (interviewee 2), and so on. These codes appear in table 11.2, shown a few pages above.

11.3. Global metrics

11.3.1. In-depth interviews

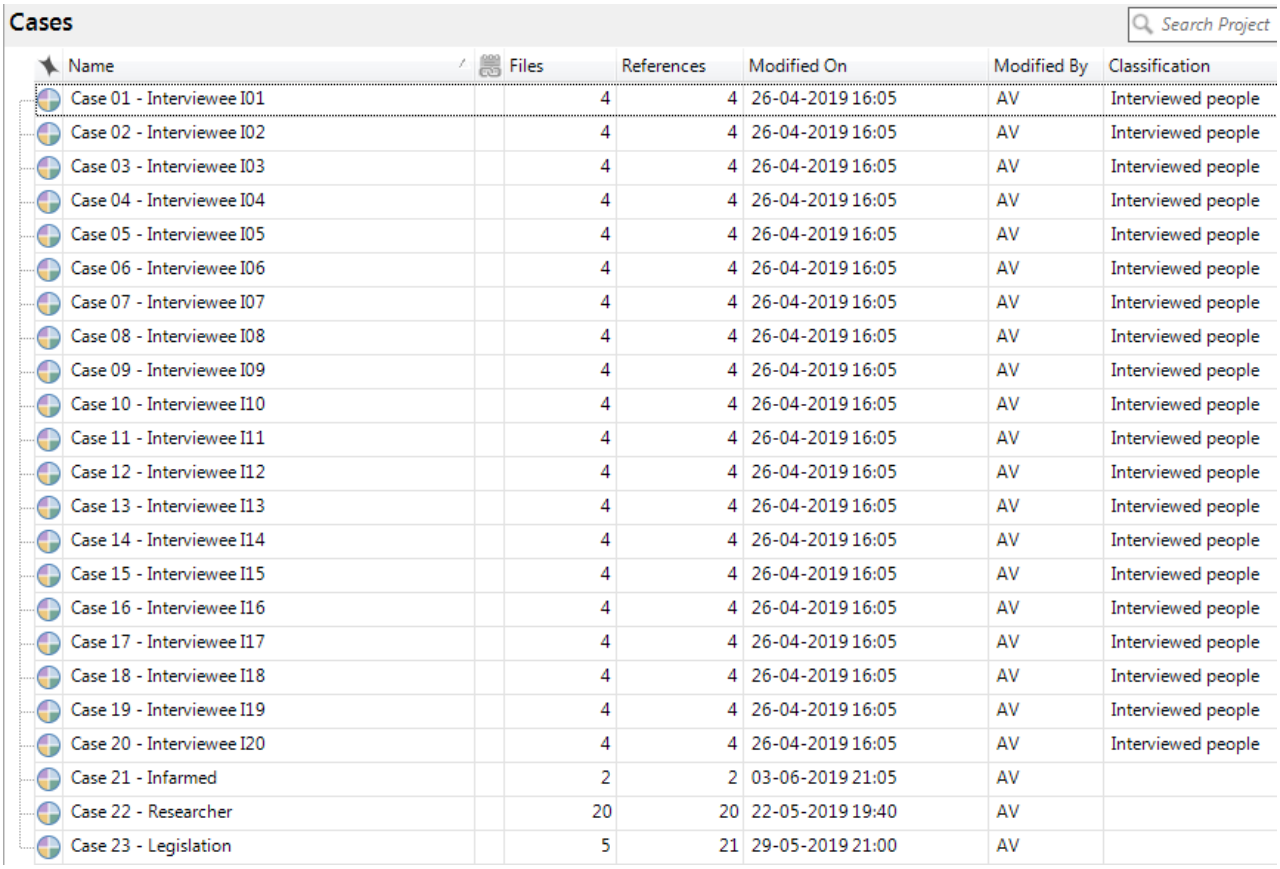
We start this sub-chapter by briefly explaining the procedures observed at NVivo. We started by uploading a series of files:

- Interviews transcriptions – 20 files
- Interviews sound recording – 19 files (two interviewed officers at Apifarma, with one single sound file)
- Researcher observations transcriptions – 20 files
- Researcher observations sound recording – 19 files
- Researcher observation transcription on Infarmed interaction – 1 file
- Researcher observation sound recording on Infarmed interaction – 1 file
- Legislation and related documents – 5 files

We then created 23 cases, one for each of the 20 interviewees, one for Infarmed, one for the researcher, and one for the legislation. We then associated each file to the correspondent case. We also created a case classification called “Interviewed people” and associated each case to

this case classification (to basically “explain” NVivo that 20 cases - interviewed people - correspond to interviewed persons).

The cases can be seen in figure 11.2 below.



Cases

Search Project

Name	Files	References	Modified On	Modified By	Classification
Case 01 - Interviewee I01	4	4	26-04-2019 16:05	AV	Interviewed people
Case 02 - Interviewee I02	4	4	26-04-2019 16:05	AV	Interviewed people
Case 03 - Interviewee I03	4	4	26-04-2019 16:05	AV	Interviewed people
Case 04 - Interviewee I04	4	4	26-04-2019 16:05	AV	Interviewed people
Case 05 - Interviewee I05	4	4	26-04-2019 16:05	AV	Interviewed people
Case 06 - Interviewee I06	4	4	26-04-2019 16:05	AV	Interviewed people
Case 07 - Interviewee I07	4	4	26-04-2019 16:05	AV	Interviewed people
Case 08 - Interviewee I08	4	4	26-04-2019 16:05	AV	Interviewed people
Case 09 - Interviewee I09	4	4	26-04-2019 16:05	AV	Interviewed people
Case 10 - Interviewee I10	4	4	26-04-2019 16:05	AV	Interviewed people
Case 11 - Interviewee I11	4	4	26-04-2019 16:05	AV	Interviewed people
Case 12 - Interviewee I12	4	4	26-04-2019 16:05	AV	Interviewed people
Case 13 - Interviewee I13	4	4	26-04-2019 16:05	AV	Interviewed people
Case 14 - Interviewee I14	4	4	26-04-2019 16:05	AV	Interviewed people
Case 15 - Interviewee I15	4	4	26-04-2019 16:05	AV	Interviewed people
Case 16 - Interviewee I16	4	4	26-04-2019 16:05	AV	Interviewed people
Case 17 - Interviewee I17	4	4	26-04-2019 16:05	AV	Interviewed people
Case 18 - Interviewee I18	4	4	26-04-2019 16:05	AV	Interviewed people
Case 19 - Interviewee I19	4	4	26-04-2019 16:05	AV	Interviewed people
Case 20 - Interviewee I20	4	4	26-04-2019 16:05	AV	Interviewed people
Case 21 - Infarmed	2	2	03-06-2019 21:05	AV	
Case 22 - Researcher	20	20	22-05-2019 19:40	AV	
Case 23 - Legislation	5	21	29-05-2019 21:00	AV	

Figure 11.2 – Cases loaded in NVivo

The next procedure we implemented was to insert the structure of the conceptual model. To do this, we created a node called “Model” → “General Data” and added additional nodes to design the structure of the model (observing the case study protocol), as shown below in figure 11.3.

Model

Search Project

Name	Files	References	Created On	Created By	Modified On	Modified By
Model	0	0	24-04-2019 12:03	AV	24-04-2019 12:03	AV
General Data	0	0	24-04-2019 12:04	AV	24-04-2019 12:04	AV
1 - Pharma comm. channels & promo instrum.	0	0	24-04-2019 12:05	AV	24-04-2019 12:08	AV
1.1 - Communication channels	0	0	24-04-2019 12:05	AV	25-04-2019 13:08	AV
1.2 - Promotion tools	0	0	24-04-2019 12:05	AV	25-04-2019 13:09	AV
1.3 - Effect of promotion tools on Rx behavior	0	0	24-04-2019 12:06	AV	25-04-2019 13:09	AV
2 - Implem. of the detailing ceiling in the NHS	0	0	24-04-2019 12:06	AV	25-04-2019 13:04	AV
2.1 - Motivations and goals of the detailing ceiling	0	0	25-04-2019 13:10	AV	25-04-2019 13:10	AV
2.2 - Implementation of the detailing ceiling	0	0	25-04-2019 13:11	AV	25-04-2019 13:11	AV
2.3 - Pharmaceutical companies reaction	0	0	25-04-2019 13:11	AV	25-04-2019 13:11	AV
3 - Effect of the detailing ceiling to the NHS	0	0	25-04-2019 13:06	AV	25-04-2019 13:06	AV
3.1 - Effect on PSRs	0	0	25-04-2019 13:12	AV	25-04-2019 13:12	AV
3.2 - Effect on pharmaceutical companies	0	0	25-04-2019 13:13	AV	25-04-2019 13:13	AV
3.3 - Effect on NHS institutions	0	0	25-04-2019 13:13	AV	25-04-2019 13:13	AV
3.4 - Effect on NHS physicians	0	0	25-04-2019 13:14	AV	25-04-2019 13:14	AV
3.5 - Goals attained	0	0	25-04-2019 13:14	AV	25-04-2019 13:14	AV
3.6 - Adjustments to the detailing ceiling	0	0	25-04-2019 13:16	AV	25-04-2019 13:16	AV
3.7 - Final comments	0	0	25-04-2019 13:17	AV	25-04-2019 13:17	AV

Figure 11.3 – Conceptual model operationalized in NVivo

Next, we created the structure of the questionnaire, inserting all 28 questions. After this, we associated, one by one, all the answers of all interviewees to the corresponding nodes, that is, to each of the questions, reaching 20 files and initial references per question, as shown below in figure 11.4:

Name	Files	References	Created On	Created By	Modified On	Modified By
Q01	20	20	24-04-2019 12:09	AV	26-04-2019 15:49	AV
Q02	20	20	24-04-2019 12:10	AV	26-04-2019 15:49	AV
Q03	20	20	24-04-2019 12:10	AV	26-04-2019 15:49	AV
Q04	20	20	24-04-2019 12:10	AV	26-04-2019 15:49	AV
Q05	20	20	25-04-2019 13:22	AV	26-04-2019 15:50	AV
Q06	20	20	25-04-2019 13:23	AV	26-04-2019 15:50	AV
Q07	20	20	25-04-2019 13:25	AV	26-04-2019 15:50	AV
Q08	20	20	24-04-2019 12:12	AV	26-04-2019 15:50	AV
Q09	20	20	25-04-2019 13:25	AV	26-04-2019 15:50	AV
Q10	20	20	25-04-2019 13:26	AV	26-04-2019 15:50	AV
Q11	20	20	25-04-2019 13:27	AV	26-04-2019 15:50	AV
Q12	20	20	25-04-2019 13:27	AV	26-04-2019 15:50	AV
Q13	20	20	25-04-2019 13:28	AV	26-04-2019 15:50	AV
Q14	20	20	25-04-2019 13:28	AV	26-04-2019 15:51	AV
Q15	20	20	25-04-2019 13:29	AV	26-04-2019 15:51	AV
Q16	20	20	25-04-2019 13:29	AV	26-04-2019 15:51	AV
Q17	20	20	25-04-2019 13:29	AV	26-04-2019 15:51	AV
Q18	20	20	25-04-2019 13:30	AV	26-04-2019 15:51	AV
Q19	20	20	25-04-2019 13:30	AV	26-04-2019 15:51	AV
Q20	20	20	25-04-2019 13:30	AV	26-04-2019 15:51	AV
Q21	20	20	25-04-2019 13:31	AV	26-04-2019 15:51	AV
Q22	20	20	25-04-2019 13:31	AV	26-04-2019 15:52	AV
Q23	20	20	25-04-2019 13:31	AV	26-04-2019 15:52	AV
Q24	20	20	25-04-2019 13:32	AV	26-04-2019 15:52	AV
Q25	20	20	25-04-2019 13:32	AV	26-04-2019 15:52	AV
Q26	20	20	25-04-2019 13:32	AV	26-04-2019 15:52	AV
Q27	20	20	25-04-2019 13:33	AV	26-04-2019 15:52	AV
Q28	20	20	25-04-2019 13:33	AV	26-04-2019 15:53	AV

Figure 11.4 – Questions insertion (nodes) at NVivo

The following step was the coding of the interviwee answers. To do this, we observed a question by question logic, exemplified below:

- We started with question number one, by reading all answers (20 respondents), and coded, in the analysis model, the main groups (or nodes) we found relevant
- Then we moved to question number two, reading all answers and then coding the relevant nodes
- We continued this analysis until we reached question number 28

During this process, we also associated interviews excerpts to the recently created nodes (codes). The coding process was interactive, given that we improved the previous coding by incorporating new insights gathered in subsequent questions. We then coded the researcher observations.

The following step was the validation of the coding process, in order to find eventual inconsistencies and improve overall logic and robustness. To do this, we fully read all the references inside each node, and performed the following corrections or improvements:

- Uncoding of "Literature" and "Informative material" references from "Mail" node (communication channels) – the references did not explicitely indicate they were sent by mail
- Elimination of the node "Less sponsorships" and included the reference in "Utilization of less expensive channels", which already had similar references from other cases
- Uncoding of "Brochures" reference from "Mailing" node (promotion instruments) – the reference did not explicitely indicate brochures were sent by mail
- Uncoding of "Presence at events" reference from "Congresses" node – the reference did not explicitly the events were congresses. A later comment from the same interviewee clearly indicated he or she was talking about congresses (and therefore instead of two references, we opted to having only the explicit one)
- Uncoding of "Internet" reference from "E-mailing" node – the reference was not explicitly enough to be considered e-mailing
- Uncoding two references of "Medical press" from "Medical literature", given that it could be more precisely coded at "Journal advertising" – in one of the cases the reference was already there (at "Journal advertising"), and in another we coded it in the proper node

- Renaming of the node “Generics shift from physicians to pharmacists” to “Generics promotion shift from physicians to pharmacists”, to better define its scope
- Creation of sub-nodes inside the node “Control patterns”, to better represent the contributions from the interviewees (with the sub-nodes “By region”, “By type of institution”, “By type of HCO leadership”, and “By temporal evolution”)
- Other amendments of lower magnitude

The result of this process can be schematically visualized in appendix 5, where we present a series of outputs obtained during the qualitative analysis with NVIVO (coding statistics, and additional tables and figures).

11.4. Results

In this sub-chapter we addressed the results of the non-structured interviews, and of the in-depth interviews (including the researcher observations and all other relevant files).

11.4.1. Non-structured interviews

The main insights gathered during the non-structured interviews with pharmaceutical industry specialists are summarized next.

- **Compulsory prescription by INN**
    - With the compulsory prescription by INN, there was an initial resistance from the pharmaceutical industry. Exceptions to the strict prescription bu INN (that is, without brand) were created, allowing physicians to select a specific brand of generics, given certain conditions
        - One was the existence of some side effects, which had to be previously reported to Infarmed (which represented a flat fall of the exception, given that the great majority of phsycians had not reported those aledged side effects previously)
        - Another was the case of chronic pathologies, given that these are the ones where physicians can justify the choice of a branded medicine (for these purposes, chronic conditions are the ones where patients are medicated for a period higher than 28 days, such as typically hypertension, diabetes, and other)
    - Pharmaceutical companies shifted their reps teams from phsycians to pharmacies. Therefore, the prominence of physicians was significantly

emptied, and the bargaining power shifted to pharmacies, which had to dispense the least expensive option from a list of three or five generics, but whenever they did not have none of these, they could ask the patient to sign the back of the doctor prescription, and thus accepting to be given other brand. Only one or two generics companies are now visiting some physicians, but mainly for prestige or institutional awereness (to demonstrate that the factories are safe, modern, and so on)

- **Compulsory electronic prescription** - with the entry into force of the electronic prescription, the NHS adapted the prescription softwares to – purposely, as underlined by the specialists we spoke with during this phase – hamper the ability of phsycians to prescribe a specific brand of generics. The systems became much less user-friendly, and physicians have to scroll down until they find the generics brand they want to prescribe, and then apparently have several confirmation boxes asking "are you sure?", "there is another option less expensive available. Are you sure you want to prescribe a more expensive one?". Some physicians initially resisted to these changes in the softwares, but finally the great majority apparently was "beaten" by the systems, because at the end of one working day those extra clicks could represent a non-insignificant amount of minutes which could be dedicated to assistencial tasks, rather than mouse clicking. Also, this option would also save doctors' patience. Therefore, the majority of physicians ended up by prescribing the first option that appears in the system, which is the one with the lower price for a particular active principle. By other words, physicians subordinated their prescription to the price of medicines and to the prescription softwares

- **Shift from ambulatory (retail) to hospital** - the main pharmaceutical companies are shifting their focus from ambulatory (retail) to hospital, given:
    - The absence of big blockbusters in the ambulatory pipeline
    - The loss of exclusivity suffered by many of the big drug brands
    - The increasing competition face by companies (other branded competitors, generics)
    - Higher profitability typically experienced with hospital drugs (Oncology, infecciology, …)

- **Excessive number of reps** – until 2010/2011, there was a disproportionate number of reps promoting drugs in the NHS. Pharmaceutical companies fought to have a high share of voice, in the assumption that this would result in a higher prescription and market share. Some territories (groups of bricks) had seven or more reps of each company, which were using mirror visits, or "Lines", as called in Portugal. This created stress on the NHS institutions and physicians

- **Economic crisis** – with the successive problems and deficits registered by the Portuguese economy, and the request for financial assistance, Portugal was intervened by Troika, which imposed several measures on the economy, including the pharmaceutical industry, which resulted in a very violent crisis also in the Pharmaceutical industry. This contributed to a strong reduction in the number of reps, starting from around 2012

- **Legislation initiatives** - there were several legislation initiatives mainly during the Government of José Sócrates, with the goal of reducing the health expenditure. These initiatives focused the prices (several compulsory price reductions), the reimbursements, the generics, and other aspects of the pharmaceutical industry

- **Higher control of marketing initiatives** – Infarmed has now the ability to control the marketing activities of pharmaceutical companies (with an investment higher than a specific amount). Companies have the obligation to register, at Placotrans – the transparency platform at Infarmed – the sponsorships, speaker fees, invitations to congresses, sponsored training, consultancy, etc, to each recipient, physicians and/or institutions

With all these changes, and in light of this new paradigm, the limitations imposed to the number of visits by Order 8213-B/2013 had a mere virtual effect, given that the previous reduction on the number of reps, the shift of the bargaining power to the pharmacies, and the other context variables referred above, had already provoked a very strong reduction on the number of visits to the NHS.

The only probable exceptions of products that may have not suffered from this new paradigm were specific classes such as oral anticoagulants such as Xarelto, Pradaxa and

others, and a few novel drugs such as new antibiotics, that still have the patent active and therefore are not suffering from the competition of generics.

When asked whether there were already limitations to the number of visits to the NHS, some of the specialists argued that some institutions – a minority - had already put in place some form of control before Order 8213-B/2013, but this was not generalized to all institutions in Portugal. Some institutions apparently had implemented limits on the daily number of reps, but there was not an effective limitation on the number of visits per year a company could make. Moreover, with the lines – or multiplication of "virtual" companies with the umbrella of a bigger company – reps could multiply their visits to the same NHS institution, by being enrolled in a few virtual companies.

11.4.2. In-depth interviews, researcher observations, and legislation

We divided the results by main dimension, and then by sub-dimension.

11.4.2.1. Pharmaceutical communication channels and promotion tools

1.1 - Communication channels

The most referred communication channels were face-to-face (with 32 references from 23 sources), digital (16 references from 14 sources), mail (11 references from nine sources), and telephone (five references and sources). These results are aligned with previous literature on pharmaceutical marketing, where face-to-face promotion investments (especially on detailing are on the top of the ranking of the pharmaceutical companies, as noted by Gagnon & Lexchin (2008) and by IMS Health (2015a). The interviewees who contributed more to this sub-dimension were physicians, PSRs and high officers (analysis by position). Interviewees I5 (physician) and I14 (PSR) were the most active in terms of number of references. The researcher was not expecting such a high number of references to the phone communication channel (teledetailing), given that it was not referred quite often by previous research in pharmaceutical marketing.

In terms of patterns in the previous five years, there is an undoubtful tendency to increase the utilization of digital communication channels (31 references by 17 sources), which appears in line with IMS Health: 3,2% of the total pharmaceutical industry investment in 2014 (IMS Health, 2015a) and 3,8% in 2015 (IMS Health, 2016). High officers from the NHS and from the pharmaceutical industry were the main contributors to this evidence (analysis by

Institution). A clear example of this tendency can be seen with this excerpt from I20: «*Digital channels will be, more and more - and despite having some limitations – the most positive way of making the information reach the physicians*». Other tendencies referred were the growing utilization of less expensive channels and less face-to-face interactions, and less materials sent by traditional mail. Three interviewees (one physician, one hospital director, and one high officer from a pharmaceutical company – analysis by position) revealed they did not see any pattern change in the previous five years.

1.2 - Promotion tools

This sub-chapter resulted in a substantial list of promotion instruments referred by the interviewees. The most mentioned one – by far – was detailing (45 references from 26 sources), which validates previous research (Yi, Anandalingamb & Sorrell, 2003; Gagnon & Lexchin, 2008; Datta & Dave, 2016). These references were particularly active in the case of PSRs, physicians and high officers (analysis by position). Other promotion instruments which complete the top five were e-mailing, congresses, medical literature, and webinars, raising the evidence for the importance digital promotion channels are gaining (two instruments in the top five). An important part of the references to e-mailing was made by physicians, as the main targets of this instrument. Other instruments were referred, with a lower magnitude in terms of references, and these include clinical meetings, journal advertising, mailing (direct marketing), e-detailing, and tele-detailing. The researcher was expecting a higher number of references to e-detailing (some interviewees alleged that there were some experiences made with this instrument, but apparently were reduced or discontinued – examples: «*There were some pharmaceutical companies – not many – which tried to contact doctors through skype*» (I15), «*there were some experiences for many companies with remote detailing*» (I18)).

Regarding the patterns in the previous five years, the top five of the references include more digital promotion instruments (17 references from 15 sources), less detailing, a higher strategic, scientific and economic focus, a higher usage of tablets during face-to-face interactions with physicians, and the shift of promotion from physicians to pharmacists (in the case of generics). These tendencies are particularly evident in excerpts of the interviewee I1, a very high officer from the ministry of health (21st Constitutional Government): «*Nowadays we talk about digital marketing and therefore digital marketing allows a number of new relationship formulas that are even more efficient, less time consuming, that dispense the*

traditional visit that was paradigmatic, for an approach more based on alternative mechanisms of communication such as those associated today to the digital era», «*Ethical aspects can under no circumstances be ignored, and therefore in the last five years we have improved the ethics of selling or the ethics of communication*», «*Marketing started to have a more strategic and more associated component to value and results, than to the mere sale of a product for a price or a price*».

These contributions were especially rich from the mentioned high officer from the ministry of health, and from high officers from pharmaceutical companies. Other tendencies mentioned include less Mailing (direct marketing), a higher focus on ROI analysis, patient benefit as the main driver (or create value to patient), create value to physicians as a partner, higher compliance and ethics, a holistic approach (targets), and resistance to non-personal Push initiatives.

As a global pattern, we can conclude that the traditional way pharmaceutical companies used to communicate with physicians (mainly based on the benefits of the product) is being substituted by a new, more holistic, scientific and ethical way of interacting with the doctors, more centered in the patient and the pathology, as partners.

Examples of this evidence can be seen in the following excerpts: «*What is important is to safeguard that this is done in a framework not only of legal and competitive legitimacy, but in favor of the patient. Patients can not be instrumented by poor communication, or by a poor understanding of the doctor's message that is transmitted to them, or by a promotional attitude I would call more aggressive or less ethically controlled, which may lead to over-prescription or inappropriate prescription*» (I1), «*Clearly the industry appears here as a partner that aims to also contribute to the improvement of the health of the population. This is undoubtedly a primary objective, which is naturally linked to the achievement of certain commercial objectives*» (I10), «*Higher rigour of the promotional practices, good practices, codes of ethics, all to ensure that the promotion activity does not become distorted. As all heard horrible stories in the past, such as people who complained about a broken nail and came out of the medical appointment with three antibiotics and two anti-inflammatories, these bizarre thinbs happened, there were those who tried to do it and there were those who would accept it. And we all have sinned. Today, honestly I think it's over. And if it exists, it should be very marginal*» (I14).

1.3 - Effect of promotion tools on prescription behavior

This sub-dimension includes several other sub-dimensions, which we analyzed separately.

Pharmaceutical companies' goals

With this topic we wanted to evaluate the extent to which interviewees would provide frontal answers, and to our surprise the great majority of the participants (except one very political answer from a high officer from a consulting company) expressed genuine and direct answers, which we divided in three groups. The first is a commercial goal (expressed in 29 references from 25 sources), to sell drugs and make a profit on that. We underline a very interesting answer from a high officer from APIFARMA: «*The commercial objective has nothing wrong with it! Obviously, it's totally legitimate. And therefore the medical visit will always have to underlie also the idea of showing what is the added value of the prescription of that particular medicine. Therefore, none of this is ethically wrong, quite the contrary, provided that the added value of the product is explained in relation to other competitors. It is always a goal of prescription. It is legitimate, admissible and legal. And the doctor has to prescribe in consciousness, knowing what he or she is going to prescribe*» (I12). The second is to share information and train phsycians on drugs and pathologies (expressed in 15 references from 14 sources), which is aligned with research from Alkhateeb & Doucette (2008) and Prosser & Walley (2003b). The great majority of these references were expressed by high officers from the pharmaceutical industry and by physicians. And a third goal, which is to substsitute the omission of Ministry of Health on training provided to physicians (11 references from seven sources). Some of the contributions were quite intense, assertive, and direct, arguing that the efforts made by the State (through the Ministry of Health, by the allowance of a number of days which can be used by physicians for their training – that they usually have to pay or to get sponsorship from the industry) appear to be insufficient to contribute to an adequate and permanent training and update of physicians of the NHS. Therefore, and following the explanation of some interviewees, the pharmaceutical industry appears to compensate this omission, by providing physicians regular access to information, novelties, studies, through PSRs, and through sponsorships to the participation in clinical sessions and congresses. APIFARMA had the highest number of references in this third goal, followed by high officers from the pharmaceutical industry. We provide two excerpts to illustrate some of the opinions on this subject, from one doctor (I02) and from a high officer from APIFARMA (I11): «*Given that the information I receive from the pharmaceutical companies is almost the only one that exists, it is blessed because of that, reason why we have to accept it, I have to accept it, and indeed accept it, the presence of the companies, because I understand that there is nothing*

better» (I02), and «*One of the things we have seen before is that the State does not fulfil, or fulfils only partialy, its obligation of training doctors. It grants doctors 14 days for their training, which is already a contribute, but not more than that (…) and the pharmaceutical companies combat the deficiency in the physicians training (…) it is important for the doctor to know the latest developments (…) there is a face (the rep) that helps him or her to respond to the insufficiencies of the State, medical training wise*» (I11).

Factors influencing Rx decisions

The main factors influencing physicians' prescription decisions, according to the primary research conducted, include drug price and economic status of the patient (the highest referred factor, with 17 references from 15 sources). This very interesting evidence follows previous research by Pitt & Nel (1988); Gönül et al (2001), Spiller & Wymer (2001) and Stros & Lee (2015). The top five of factors also include the quality of the product (in line with Venkataraman & Stremersch (2007), Fischer, Leeflang & Verhoef (2010), Stros & Lee (2015)), evidence & literature & guidelines (in line with Aronson (2006) and Huskamp, Epstein & Blumenthal (2003)), the relation with PSR and the pharmaceutical company (in line with Pitt & Nel (1988), and Stros and Lee (2015)), and own experience and habit (in line with Pitt & Nel (1988), and Spiller & Wymer (2001)). This last factor is mostly evident in the following excerpt: «*Doctors tend to keep a portfolio of their own products, because they manage them well, give them security, do not have major problems, doctors have in their heads two or three or four standard analgesics, antipyretics, have a few antibiotics (…) there is a portfolio, which is personal*» (I1).

Other factors influencing prescription behavior include the physician profile, peers & scientific societies, the prescription software (in the scope of prescribing restriction policies highlighted by Spiller & Wymer (2001), and Schumock et al (2004), trust, confidence and prestige (pharmaco) (Pitt & Nel, 1988), adequacy to the clinical status, simplicity to the patient, and the patient him or herself. Two relevant analyzes can be made here: one regarding product quality, and one regarding physician profile. We divided the references related to quality into eight attributes, here listed: efficacy in terms of results to the patient, safety & minimal side effects, quality in general, drug backed by research & innovation, drug has proven its worth, precise indications & treatment breadth, added value, and fast & lasting effect.

We believe this division provides a better understanding of the umbrella word quality. Physicians were the highest contributors to the references regarding the quality aspects, and one of the top three contributors to the factors influencing prescription decisions, alongside with high officers from pharmaceutical companies and PSRs. Regarding physician profile, based on the analysis of the interviewees we were able to divide the references into five categories: there are many physician profiles, university where they got their degree, attitude in relation to the Rx of new drugs, GPs vs Specialists, and younger vs older physicians. The second of these categories was quite unexpected since to the extent of our knowledge it has not been addressed by previous research.

An interesting excerpt sheds light on this: «*First, there is an important factor that clearly is the school (university) to which the doctor belongs (Lisbon, Coimbra, Porto), and this is often perfectly noticed in the performance of the products, ie a certain product in Lisbon can have a certain performance and then we'll see in Porto and it's completely the opposite. We often look for the reason for this, and one of the reasons, of course, is that we realize that in that school specifically the University of Porto or the University of Lisbon there is an understanding that the treatment should be done in the form A and in Lisbon they understand that it must be done in the form B*» (I10).

The third category evidences the attitude in the prescription of new products, whether the doctor is more innovator or more conservative, and the fourth suggests that GPs and specialists may have distinct attitudes in the prescription («*There are doctors who are conservative and like to keep their prescription, such as some GPs*», I16).

Influence of promotion instruments on prescription behavior

Only one interviewee (I11, from Apifarma) declared that promotion instruments do not have an effect on prescription behavior. The general evidence is that these instruments have an effect on physician prescription behavior (12 references from 12 sources), of which five from PSRs. This influence can be detected in some of excerpts, such as «*Historically, yes (promotion instruments do influence prescription behavior). To see that we can analize the pharmaceutical market and its evolution, where several approaches were taken*» (I10), and «*Clearly, yes (promotion instruments influence prescription behavior*» (I17).

We then analyzed the ways this influence can be expressed, and a series of reasons appeared. The most referred one was through novelties (where pharmaceutical companies and PSRs bring physicians (studies, presentations, products), which is very clear in the contribution

from a doctor, manager of a group of health centers in the Lisbon area: «*(the influence) Mainly thought the novelties. Nobody likes not knowing the novelties, and the novelties naturally bring the will to try. It's very obvious the effort that has been made in relation to certain drugs, such as oral antidiabetics, oral anticoagulants, etc*» (I02).

Other reasons to explain this influence include the assistance of physicians in their prescription decisions, the power of persuasion, the reduction of prescription risk of physicians, and awareness rising of the pathology.

Most influential promotion instruments

In this topic, and given that we are using a qualitative approach, we were not able to quantify the comparative influence of the promotion instruments listed by the interviewees. Therefore, we present here, by descending order, the tools by number of references. The most referred tool was, by a comfortable margin (26 references from 25 sources), detailing, which, despite the different scopes (qualitative vs quantitative research), is consistent with previous research conducted by Narayanan, Manchanda & Chintagunta (2003), and by Kremer, Bijmolt, Leeflang & Wieringa (2008). In second, third and fourth places in number of references there are congresses (19 references from 19 sources), clinical meetings (13 references from 13 sources), and medical literature (six references from six sources).

The last places in terms of number of references are journal advertising, e-mailing and webinars. It is not a trivial exercise to compare these tools against tools addressed by previous research, given the noted differences in methodology, but also due to the different aggregation of promotion instruments used by other researchers. When we analyzed these evidences in light of the characterization variable position, there are clearly much more references coming from PSRs and physicians (15 out of 26 references, which compares to 10 out 20 interviewees).

Importance of detailing to pharmacos

Now entering into detailing as a promotional instrument, very stimulating evidence was gathered. Detailing has a decisive importance to pharmaceutical companies given that it allows them to explore the relation, the friendliness and friendship, and affectivity between their PSRs and the physicians they visit. This evidence received 32 references from 15 different sources, and was particularly more obvious among PSRs (the major contributors, with 17 references) and physicians (nine references). Some excerpts from two doctors are

very revealing of this aspect, such as «*(…) we create empathy, friendship, and then when we have two or three similar drugs, surely our preference will go to the one from the rep we establish a better connection with, a personal and friendship relation*» (I04), and «*I prescribe what I know, from the rep I have a closer proximity with, the relational component, the friendship (…) yes, it is important, there is affectivity over the years*» (I06), and «*Many years ago, back in the day, my daughters were little girls and my colleagues' kids were also small. They grew together in many convivialities extra work organized – and I don´t mean sponsored – by pharmaceutical companies, and we had a very close relation with reps, which now we don´t see anymore. At all!*» (I06).

The importance of PSR friendliness was previously addressed by Andaleeb and Tallman (1996). Another reason to justify the importance of detailing to pharmacos is the exploration of reciprocity, previously addressed by Roughead, Harvey & Gilbert (1998) and Katz, Caplan and Merz (2010). Some of the most relevant excerpts include, from one physician and one PSR: «*The big pharmaceutical multinationals helped me a lot in my career, by providing easy access to information, helping me to go to congresses, to which I would not be able to go without their support (…) so if there are five similar products, which one will I prescribe?*» (I05), and «*(…) there is reciprocity, and confidence. The common goal is to treat the patient the best way possible, and there is a relation of reciprocity there. I give information, the doctor receives it, the doctor reaches me with doubts, I clarify him or her, and if the doctor feels he or she has a partner helping him or her to get an adequate, impartial answer, then a relation of confidence will be set and the relation will grow, which is critical*» (I13).

Doctors and PSRs were the profiles (in terms of the characterization variable position) with the highest number of references regarding reciprocity (six each one). Another reason pointed out during the fieldwork was the personal contact (face to face) with the physicians, previously addressed by Prosser & Walley (2003b), in the sense that physicians retain information better in a face-to-face setting.

The fourth and last reason to justify the importance of detailing to pharmacos was the fact that detailing allows the maximization of the share of voice (SOV), very evident in the following excerpt from a senior consultant: «*Starting from the basics, detailing is important because when my products are being promoted during the visits, other products are not, and this is a very important aspect, which is to occupy space*» (I20). The concept and importance of share of voice were addressed by Zolterns, Sinha & Lorimer (2004), and Kumar (2015).

Importance of detailing to physicians

The importance of detailing to physicians can be seen in four reasons. The first two ones are the fact that PSRs provide novelties and continuous training (19 references from 13 sources) and provide convenience (through direct and quick access (32 references from 12 sources)). These reasons were previously discussed by Alkhateeb & Doucette (2008) and Prosser & Walley (2003b), and by Chimonas, Brennan & Rothman (2007). An excerpt from a physician is revealing of this importance: «*I must thank to all the pharmaceutical companies that helped me to improve my professional career, because they gave me much more training than the State! Had it not been for the labs, clinically I wouldn't be who I am today; I wouldn't have the capacity to be who I am, as a doctor. Therefore I would give a thank you to the labs that helped me on that*» (I06). The main contributors in terms of references were the phsycians (11 references).

Other reasons to justify the importance of detailing to phsycians include the reminder to older products, and the preference for personal contact (the latter referred by Prosser & Walley (2003b)). One interesting pattern we were able to detect, which we consider novel to the extent of our knowledge, is the clear distinction between younger and older physicians in their attitude towards detailing. Younger physicians – systematically identified by interviewee as having up to around 45 years old – tend to give a lower importance to detailing, being more difficult to reach by PSRs. As some PSRs and physicians noted, younger physicians tend to be heavy users of the internet, on-line communities where they share and dissecate new scientific articles, tend to have lower social and interaction abilities when dealing with patients, and only open their doors to PSRs when they need a sponsorship to a specific event such as a congress, but right after that event they tend to "forget" the sponsor and close the door to their detailing initiatives.

Younger phsycians appear to be more sensitive to discuss the pathology rather than the product, and seem to be more sensitive to discuss medicine of evidence. In contrast, older physicians (systematically identified as having more than 45 years old) tend to appreciate the visits of PSRs, tend to value their regular assistance, since they are not as agile in seeking information on the web as their younger peers. Some excerpts are particularly clarifying about this attitude of younger doctors, such as «*Those younger doctors don't need to speak with the rep, and don´t even need to speak to other doctors! They don´t suffer from any doubt! Those doctors from Google, from the web, with less than 45 or 40 years old. I do urgencies and I see that. Back in the day, when I was doing urgencies I used to ask my older colleagues for an*

opinion, and now the younger doctors don´t need any opinion at all! They look into the evidence A, B and C, and that´s it. They go to Google, they check the level of evidence, and know everything» (I06), and «*Nowadays new school doctors are smartphone doctors, they use tables, the web, while old school doctors typically receive information through the industry (reps) or through congresses, and that's it!* » (I10).

Also, regarding the attitude of older doctors we selected the excerpts «*Old school doctors, who were all their professional life in contact with the pharmaceutical industry, are persons much closer to the industry, because they grew with the industry, the industry participated immensely in their medical training. And this is quite evident today, where the rep has a much higher access to those doctors*» (I10), and «*Doctors older than 45 years old give a high importance to detailing, since detailing is a part to their daily activities, of their training, of their knowledge recycling, of their update*» (I14).

Importance of detailing vs different product scopes

Detailing is perceived as more effective in the case of originator drugs, as opposed to generic drugs. This perception was particularly expressed by physicians and by PSRs. Some reasons for that include the fact that there is no point on continuing detailing doctors after a drug loses its patent, given that pharmaceutical companies will move their investments to the pharmacy channel, visiting pharmacists. The following excerpt enriches this perception: «*No, (the importance) is not the same! It is higher regarding an innovator, or that at least appears in the market. Older products do not visit us anymore (…) nobody speaks about them anymore!*» (I03).

Detailing is also perceived as more effective in the case of younger versus older drugs. This perception is validated by previous research conducted by Narayanan et al (2003), Manchanda, Rossi & Chintagunta (2004), Manchanda & Honka (2005), Narayanan et al (2005), Dave (2013), and by our own research. Two revealing excerpts are now shown, from one high officer from a top pharmaceutical company (I09) and from a physician (I04): «*The importance and interest (of detailing) is higher for new drugs. It makes more sense in new drugs than in old ones widely used and known and where there are many therapeutic alternatives, and where these visits become noisy, do not truly add value*» (I09), and «*Detailing old products does not make sense at all! The medicine is well known, there no use of having the reps pam pam pam, "stepping" the message, there are such reps very annoying,*

very boring... I apologize for introducing this language in your interview (laughs), but those reps are really like a mosquito» (I04).

Doctor self-perception of detailing influence

One relevant aspect we wanted to understand was doctor perception of the influence of detailing on their prescription decision. All seven physicians (five practicing physicians and two high officers from one hospital and one health center) noted that detailing can influence their prescription behavior. This evidence is somewhat converse to previous research conducted by Steinman, Shlipak & McPhee (2001), where they found that 60% of the physicians stated that pharmaceutical industry promotions and contacts did not have influence on their own prescribing. However, we do note that our sample is substantially smaller, and that additional research would be necessary to more clearly understand this topic, with a higher sample. The ways this influence is expressed, according to the seven interviewed doctors, includes five topics: they are influenced whenever PSRs bring them novelties, they are influenced due to the affective bond with reps, by reps alerting them to some specificities about the promoted drugs, by reminding them about the product, and by clarifying doubts (again, the principle of reciprocity addressed above is present). The following excerpt illustrates the recognition of the importance of affection, by a physician: «*Yes it influences, by the help in training, by the relation with the rep, by the affective component*» (I06). Curiously, one of the doctors, who as a first reaction stated that he was not influenced at all by detailing, later in the interview he admitted it can influence him by reminding him about existing products, that therefore can be chosen by the physician from a group of a few medicine alternatives.

Doctor perception on comparative influence vs peers

Another interesting aspect that we tried to capture during the fieldwork was the opinion of phsycians in relation to their perception of relative influence regarding detailing, in comparison to their peers. Five physicians argued they do not know how they compare to their peers, detailing influence wise. The other two phsycians argued that they are less influenced than their peers, which appears to be consistent with previous research developed by Sah & Fugh-Berman (2013), where physicians appeared to perceive themselves as more "immune" to detailing then their peers. Curiosly, these two physicians are the high officers from the NHS pointed above.

Importance of new PSR competences

A sub-topic that appeared in our research, which was not present in our script, addresses the importance of new PSRs competences, due to the changes that the Portuguese pharmaceutical market faced in the previous years. New PSR competences include the ability or sensitivity to evaluate the profile of each physician and adapt the approach and speech accordingly, which is aligned with findings from Rozell & Newman (2010) and Stros & Lee (2014), which underline the importance of the PSRs personality, emotional intelligence and customer orientation. New competences also include transparency and honesty in the sense that whenever he or she does not know how to answer a question he or she will say it. The ability to be didactic, be less aggressive, and engage into a good involvement with the doctors were also new PSR competences underlined during the fieldwork.

Four of the five contributors to these insights were physicians, as the main evaluators of PSRs evolution over time. An explicating excerpt demonstrates some of the evidences described above: «*I notice that lately reps are more informative, they bring (new information), they add value. This morning I had a presentation, and they are not really as aggressive as before, they do not make the suggestion to prescribe, except for one exception here and there, but I do not think they are so aggressive. Now they are more didactic, they try to bring more information, and therefore it is even more appealing to listen to them, I find them more informed, and in some areas they are much better prepared*» (I08).

Synthesis of the main findings – Dimension 1

The main communication channel used to interact with physicians is still, by far, face-to-face, followed by digital, mail, and telephone. Whereas the market has been evidencing a reduction in the utilization of face-to-face, the digital channel has been growing especially since the beginning of the decade. Mail and telephone channels importance is being reduced.

The most mentioned promotion tools currently being used in Portugal to promote medicines to physicians are detailing (as the clear leader, but losing some importance), e-mailing (which has been growting substantially in the last years), congresses, medical literature, and webinars (also noticing a growing utilization by pharmaceutical companies). Other instruments used include clinical meetings, journal advertising, mailing (tendentially falling into desuse), e-detailing, and tele-detailing. Physicians – especially the younger generation – are more open to the use of digital promotion tools such as e-mailing, webinars and e-detailing.

Pharmaceutical companies' main goal is to sell drugs (commercial goal), recognized as legitimate given that they are private companies operating in a competitive market, subject to a strict regulatory and ethical framework. Other goals include sharing information and train physicians on drugs and pathologies and substituting the State in the task of training NHS physicians.

The main factors influencing physician prescription decisions include drug price and economic status of the patient, the quality of the product (including efficacy, safety and side effects, backed by research, innovation, precise indications, treatment breadth, fast and lasting effect), evidence, literature and guidelines, the relation with PSRs and with the pharmaceutical company, and own experience and habit. Other factors include the physician profile (including the university where they had their graduation, their specialization, their attitude, and their age group), peers and scientific societies, the prescription software, trust in the pharmaceutical company, adequacy the clinical status, simplicity to the patient, and the patients him or herselves.

Promotion instruments can have a strong influence in physician prescription behavior, as noted by the great majority of interviewees, including all the PSRs, and this influence is consubstantiated by bringing novelties to physicians (new drugs, new studies), by persuasion, by the reduction of physician prescription risk, and by raising the awareness of pathologies.

According to the insights gathered from the interviewees, the most influential promotion instruments are detailing, congresses, clinical meetings, medical literature. There were also references to journal advertising, e-mailing and webinars.

Detailing is a very important promotion instrument to pharmaceutical companies, allowing them to explore the relation, the friendliness, friendship and affection between PSRs and physicians, and this evidence was backed by the majority of the interviewed physicians. Detailing also allows companies to explore the power of reciprocity, by providing easy access to information, and to explore the influence of the personal contact, given that many phsycians retain information better in a face-to-face interaction. Also, detailing allows the maximization of the share-of-voice.

Physicians tend to value detailing given that it allows them to receive novelties and continuos training from pharmaceutical companies, providing convenience and reminding older products. Physician age group appears to have a strong impact on their attitude in relation to physicians. While older physicians (>45 years old) typically seem to have a closer relation

with the pharmaceutical industry and tend to value the assistance and regular presence of PSRs, younger physicians seem to attribute less importance to detailing, searching information in on-line communities, on-line journals, and at search engines, more focused on evidence than on the speech of PSRs.

This is a challenge to the industry, to find the best approach to marketing and sales activities, adapted to these two very different doctor profiles. Detailing is more effective in the case of originator drugs (in comparison to generics), and more effective in the case of younger drugs (in opposition to older drugs). Doctors are aware of the influence of detailing on physician prescription behavior, and all admitted they can be influenced too. Two of the five physicians argued that they are less influenced than their peers, regarding the effect on detailing on their prescription choices.

There is a growing importance of new PSR competences, including the ability to evaluate the physician profile, customer orientation, transparency and honesty, to be didactic and helpful, avoding commercial pressure on physicians. Interestingly, PSRs appear as the highest defensors of detailing, its importance, its usefulness to physicians, and its ability to impact physician prescription behavior. Perhaps these opinions may be somewhat biased given that the PSRs were defending and justifying their own "survival" in the industry, but the contributions appeared to be very genuine, direct, signaling that they strongle believe – and feel in the practice – their importance.

11.4.2.2. Implementation of the detailing ceiling in the NHS

Introduction

By memory, we remind that there was already a detailing ceiling in force (Order 9630/2001, 11th April), but according to non-structured interviews conducted at the beginning of our research its application and control was not generalized through the country, and did not have a unique, centralized national control system with fixed criteria (Regional health administrations should establish standards for access to the facilities of hospitals and health centers).

Order 8213-B/2013 (24th June) gave this national scope and clear and specific control procedures such as the obligation to register PSRs at Infarmed, a room dedicated to PSRs, and other specificites such as the existence of a responsible person in HCOs dedicated to the

scheduling of visits and their control. Thses evidences are particularly clear in two contributions of a high officer from APIFARMA, with direct experience since the end of the decade of 1990 with legal activity from the successive ministers of health: «*What does this 2013 Order improve? A better control in hospitals and health centers, with the need for someone to have the responsibility of scheduling medical visits and controlling that scheduling*», and «*Infarmed did not want to control the PSRs because it was not within their competence ... but it ended up assuming this function at the request of the then Minister, a little unwillingly, because they centralized everything, instead of everything being dispersed by ARSs. It was the entity that could centralize this situation. From the moment INFARMED centralizes, I think that control starts to be more effective, because it ceases to be a paper, a list, an agenda that was easily scratchable, changeable... 'take that name and put mine...'*» (I12).

The evidence of a previous detailing ceiling can be reinforced by contributions from some participants. When asked whether there was a previous detailing ceiling in place, we obtained confirmation from ten references (eight sources), but either the control was not generalized (six references from six sources) or there was not control at all (two references from two sources), also suggesting that each ARS (regional health administration) set their limits which were typically not generalized and national («*Regional health administrations should establish standards for access to the facilities of hospitals and health centers, which will be duly publicized and respected by PSRs*» (Legislation). Four references (from three sources) suggested that there was not detailing ceiling in place previous to Order 8213-B/2013.

2.1 - Motivations and goals of the detailing ceiling

Main goal

We were able to find eight main goals of the implementation of the detailing ceiling in 2013 (Order 8213-B/2013, 24th June), some of them somewhat related, but differentiated enough given the contributions of the interviewees.

The most referred goal (with 30 references from 21 sources) was to reduce disturbance on health care organizations (HCOs) provoked by the presence of the PSRs. This can be seen on the following transcription excerpts: «*I would not devalue a thing that I myself have also tried to improve in my mandate, which is the massive pressure of PSRs in health institutions, (given*

that) it is a factor of enormous disturbance» (I01), «*(…) multitude of PSRs in the service and patients that are simultaneously the ones who will be the target of this... Anyway, it does not make sense. Let's just think a little, it's a fair! And a fair is what we need the least in a service with good competence*» (I02), «*everything was in excess, it looked like a fair (…)*» (I08), «*The aim was, in both Health Centers and hospitals, to avoid an amalgam of PSRs present in the various institutions*» (I12), «*I think it had to do with a regulatory effort that had to be made, because there was a lot of pandemonium up to that time ... I got to a health center to work and were 12 PSRs there (…) Aim to regulate, to avoid exaggeration, to avoid this nonsense*» (I14), «*I believe that the industry was to blame for this, because I remember being seven or eight PSRs in one HCO, it seemed a concentration for coffee rather than a health area*» (I16), «*The goal was to end the savagery. There was no control! Imagine a corridor with eight or 10 PSRs! Often there was no privacy in the space where the doctor spoke with us, because they were patients there, all mixed up, it was not discrete at all and caused a great confusion (…) There were chaotic places*» (I17), «*It was an exaggeration. That is, it was an exaggeration in terms of the number of PSRs who walked in the institutions of the National Health Service*» (I18). We can summarize some of the words associated with this goal: **massive presence of PSRs**, **disturbance**, **multitude of PSRs**, **a fair**, **excess**, **amalgam**, **pandemonium**, **exaggeration**, **nonsense**, **concentration**, **savagery**, **confusion**, and **chaotic**.

The second most referred goal (with 27 references from 19 sources) was to reduce prescription (especially on newer, more expensive ones) and consumption, which reveals a very lucid and interesting perception that to an increase in the detailing intensity there can be an increase in prescription. Scientific articles in general were even referred by a few interviewees, as a proof of this relation (especially by a former high officer from the Ministry of Health of the 21st Constitutional Government, PhD qualification). Some of the most revealing transcription excerpts evidence this goal: «*(…) on the other hand because there was the perception - which I believe to be legitimate – that an overpushing in terms of promotional activity - and this comes in the literature – will induce more prescription*» (I01), «*I think it must have been in the sense of curbing what they (tutelage) obviously knew, that these visits influence prescription*» (I03), « *(…) lower prescription, and lower consumption*» (I05), «*(…) probably to lower prescription of newer and brand-name drugs*» (I08), «*Reduce spending on prescription, on the assumption that a higher number of PSRs visits is equivalent to a higher consumption of more expensive drugs and higher costs with reimbursement. No doubt about that*» (I14), «*The main thing I think was economical, because I remember several years ago that studies appeared suggesting a correlation between the promotional activity of*

detailing and sales (prescriptions)» (I19). Curiosly, PSRs were in the origin of the highest number of references regarding this second goal, suggesting that they do know the impact they can have on the prescription behavior of physicians they visit.

The third most referred goal (with 16 references from 15 sources) is related to the second: reduce commercial pressure of pharmaceutical companies (through their PSRs) on physicians. We opted to separate the second and third most referrerd goals given that the third is more generic, broader scope (reduce commercial pressure) and the second is more specific (reduce prescription). Some excerpts where this third goal is evident include «*The implicit goal was to reduce the commercial pressure*» (I01), «*(…) avoid the excessive number of PSRs visits*» (I09), «*the goal was clear: to limit the promotion space of the industry*» (I09).

The fourth most referred goal (21 references from 14 sources) was to safeguard HCPs care-related activity, allowing more time for assistential tasks, taking care of patients, instead of taking a non-insignificant amount of time dedicated to receive and excessive number of PSRs. Very interestingly, we found no contribution from PSRs to this goal, and the highest number of contributions came from physicians (nine references) and high officers (10 references, of which four from a high officer from the ministry of health very active in terms of health policy). Some of the transcription excerpts include «*Do not harm the activities of care which, for me, is the most important aspect, do not harm the care activities or the patients rights (…) … do not interfere in the doctor-patient relationship and the quality of care*» (I01), «*Restrict the time PSRs may contact with doctors, so that it cannot take time dedicated to clinical activity*» (I04), «*Improve productivity (of doctors) (…) And the time PSRs 'stole', if we think a visit from a PSR can take ten minutes ... if we think about it... if I have three PSRs, it's 30 minutes. If I have five PSRs, it's about one hour you get lost there, from one to the other. An hour of work a day is a lot of work that gets lost per day*» (I05). Order 2013 preambule itself explicits this fourth goal: «*The purpose of this Order is to establish the general rules governing the access of PSRs to NHS establishments and services and their contact with health professionals. In this way, the aim is to create the necessary conditions so that this activity does not interfere with, or in any way interfere with, the normal activity of the services, namely with regard to the provision of health care*» (Legislation).

The fifth most referred goal (25 references from 14 sources) was to discipline and dignify access to HCPs and HCOs. Many interviewees noted that an excessive presence of PSRs in the NHS institutions was also negative for PSRs, to their planning, to their work, and to their dignity, given that they were not able to perform their job with the minimum conditions

(confusion, noise, not dedicated space). For instance, this Order from 2013 foresaw the obligation of HCOs to have a dedicated room of space where PSRs could speak to physicians. Evidence from this fifth goal can be found in the following transcription excerpts «*The purpose of the 2013 Order was first to discipline, to introduce some balancing and some common sense (...) so that there could be a period outside the assistance activity, and reserved areas, with a limitation of PSRs presence (...) even from the point of view of the dignity of the professional relationship, the work of industry professionals with physicians*» (I01), «*The goal was to normalize things a bit, because sometimes it would be too much. In other words, to define a norm, equality for all (...) There was some inequality between laboratories, in the access to doctors, in the opportunity for relationship, and thus this became more standardized, more equitable. Larger pharmaceutical companies were privileged, before*» (I06). This fifth goal can also be seen in the preamble of the Order: «*(...) ensure the necessary balance between the need to disseminate this information to health professionals in service in the establishments and services of the National Health Service, and the regular functioning of the same establishments and services*» (Legislation).

The last three goals received a lower number of references, but even though provide unique insights on the perception of inerviwees on the goals of the 2013 Order: calm public opinion (six references from six sources), stimulate the prescription of generics (seven references from four sources), and stimulate the usage of digital promotion channels (three references from two sources). Regarding the sixt goal, the following excerpts are revealing: «*We often received complaints, complaints from patients, because they were waiting for the consultation, and because the PSRs entered first to speak with the doctor, and the industry itself is aware of this*» (I01), «*(...) the public opinion and the news that were being posted. I think this story, this image… I think doctors would also never be very happy with this, regarding the sponsorship they had, the trips and all these things… (...) the tutelage said 'Okay my friends, let us try to regulate this a little'*» (I03). Interestingly, four of the references had origin in interviewees working at the NHS only. In relation to the seventh goal, we underline the excerpt «*To minimize the impact of the companies' efforts, in order to encourage the adoption of generics, faster*» (I18).

2.2 - Implementation of the detailing ceiling

Booking process

This topic was not address directly on our script, but appeared systematicall during the interviews, and therefore we opted to give it visibility. The first evidence is that PSRs have to registery themselves at Infarmed, as foreseen by the 2013 Order (eight references from seven sources), here seen at a transcription excerpt from a high officer from APIFARMA: «*As soon as the electronic registration becomes mandatory in Infarmed, the companies to which they are contractually bound have to register the names of the PSRs ... I think that from then on it becomes simpler, because the hospitals that have access to databases, whether the PSR is registered or not. And then it starts to be electronic*» (I12).

Other contributions to this evidence are expressed also in the following two excerpts: «*We use an Infarmed website where we have a number, a name and a company, and it is in this portal that the number of visits we make to the establishments is marked*» (I16), and «*Article 3 - Registration, accreditation and identification: 1 - The accreditation of SIDs is obtained by registering with INFARMED*» *(Legislation).* And the second is the need of PSRs to book their visits at NHS HCOs, typically with administrative staff or security, also as foreseen by the Order, in its article 6 – Visits scheduling: «*1 - The appointment of visits in each establishment or service of the SNS is made in advance to the administrative staff that the respective head of the service indicate, in order to ensure its weekly schedule, being registered the identification data of the PSR, as well as the laboratory they represent*» (Legislation). The great majority of contributions in terms of references were PSRs and physicians.

Access process inside NHS institutions (HCOs)

This topic was also not addressed directly in the script, but since it was referred by a substantial number of interviewees we opted to include it as well. We basically found three main topics: access cards are given to booked PSRs, security guards or administrative collaborators check whether the PSR is booked, and the fact that not all HCOs have allocated a room where PSRs and doctors can speak. A director of a group of health centers contribution was particularly revealing regarding the first topic: «*There is an ID card, there are a limited number of ID cards, which are assigned to the PSRs who made the scheduling and therefore the HCO only receives the maximum limit of the number of PSRs per day, according to the detailing ceiling Order*» (I02). Regarding the control check, a physician from a health center in Algarve explained that «*In the Health Center I work at this is done by*

the security officer, he was asked not to let the PSRs enter and walk to speak with the doctors without being scheduled, and the security carries out this control at the entrance of the Health Center» (I07).

Ceiling implementation process

In this topic we wanted to understand whether the process of implementing the ceiling foreseen by Order 8213-B/2013 was put in place or not. Somewhat out of surprise, we realized a very low number of references to the full implementation of the ceiling (five references from five sources, from one consultant, three physicians and one high officer from a NHS HCO), here exemplified with the contribution of a director of a group of health centers in Lisbon: «*Yes, it was implemented here. Every now and then I go through the scheduling and I see that! And the security guards are very... Of course the PSRs have some conversation with the security guards and so they have some familiarity with them... But since the security guards are not always the same... turns out to be difficult to create a relationship...*» (I02).

The main conclusion, based on the contributions of the interviewees, is that the ceiling was implemented partially only (15 references from 13 sources). Examples of this evidence can be seen in the following transcription excert: «*I think it depended heavily on institutions. There were institutions that implemented the process scrupulously, and were those that even communicated the prevarications, because there is always! There were institutions that were a little more permissive and that gave less importance to the Order (…)*» (I12).

There were then four references (three sources) suggesting it was not implemented at all, including one clinical director of a big hospital in the area of Lisbon: «*In this case, I have to say that no limitation was implemented. What we have done in our regulation (which has not yet entered into force at the time of the interview) was to follow exactly what was recommended in the Order, and obviously there will be situations that we consider to be exceptional. There may always be one exception or another...*» (I03). There were then three references (three sources) to the fact that the implementation of the ceiling was not taken seriously: «*In general, Orders are a virtual thing in the midst of thousands of other things that come in Diário da República. No one cares too much*» (I14), «*We know this is written but it was something that was not followed very much*» (15), and «*I think the pharmaceutical companies did not give much importance to that. In our country, regulation is weak*» I19).

Ceiling control process

In this sub-dimension our goal was to understand whether the ceiling control was made, and if so whether it was effective. The main evidence was that the ceiling is not easy to control (18 references from 16 sources, mainly from PSRs and physicians), here expressed in these transcription excerpts: «*I would say (…) that (the ceiling) it is not very easy to control*» (I03), «*I honestly doubt whether it was strictly controlled, and probably at the time there should be flaws*» (I07), and «*No, it was not controllable, it does not make any sense*» (I13). The second main evidence suggests that different institutions had different control approaches (19 references from 12 sources, interestingly mainly from PSRs and high officers from the pharmaceutical industry, and less from physicians – the likely reason may be that the former have a more broader view of the industry, given that they are in contact with several physicians and institutions, being able to more clearly detect patterns).

The analysis of transcriptions reveals that there was not a unified, similar control process from institution to institution, in several aspects: the existence of a control of booked visits, the number of PSRs able to be at the institution every day, the need to identify the physicians to be visited, and other procedures, which can be seen in the following excerpt: «*It depended heavily from institution to institution and this varied greatly... and those less rigorous institutions... In that sense, let us say that the law had no effect in some places*» (I18).

One interesting aspect is that there seems to be extremes in the interpretation and application of the Order. Some PSRs alleged that, by the one hand, some HCOs do not perform any control to the presence of PSRs, and by the other hand, some HCOs took a convenient interpretation of the letter of the Order, to basically signal pharmaceutical companies that PSRs are not welcome at all. This last evidence can be encountered in two transcription excerpts: «*Here in Cascais, there is a very restricted schedule that is horrible, it's from 3:00 p.m. to 4:00 p.m., but they do not control if there are 3, 4, 5 or 10 PSRs there. The Amadora-Sintra Hospital... I think they replicate the Order obsessively, the PSRs do not go in, we can't perform our work there because they interpret... they say they are two PSRs per day (to the whole Hospital), but in good faith they have to accept two PSRs per service per day, they can not impose a limit of two PSRs on the entire hospital. But Amadora-Sintra only allows two PSRs per day, this number of times (six) per year. That is useless, it does nothing, it's the same as saying to people (PSRs): do not come here! Do not enter here!*» (I14), and «*For example the Health Center of Lapa, I remember that it had a clearly prohibition and was very restricted, it was by appointment and nobody entered there and the security guards were*

*strict. The USF Fernão Ferro has written "**No entry to dogs and PSRs**" (laughs). Yes it does! There are extreme situations*» (I19).

The next evidence helps us to understand the previous two aspects: some institutions have no resources to fully control the ceiling (13 references from eigth sources). Some of the interviwees explained that when there are hardly sufficient administrative people to assist patients, it is very difficult or even impossible to allocate someone to the control of PSRs' presence, especially in smaller health centers that do not have security guards.

This is quite clear in the following excerpt from a physician working in a health center in the Center region (I05) and from a high officer from APIFARMA (I12): «*In some hospitals and some health centers this can happen (ceiling control). But where? In those who have security guards. Those who do not have security guards, how do they do this? You get an administrative employee to take care of that? There are no employees to do the normal jobs, let alone to do this! The employee either is taking care of this, or taking care of citizens, helping them to solve their problems. So let's not have any illusions: a health center that has two floors, that have the left wing, the right wing... how are you going to control this?*» (I05) and «*The control was created, but the problem was what I was saying: there has to be someone in the institutions who makes the records, and there is a reduction of administrative staff, and the scheduling is not made, no one knows if the PSRs appear six or more times a year. The only thing that is controlled is the registration in Infarmed*» (I12). This evidence was especially present in the interviews with PSRs (seven references).

Also, there were references (four, from three sources, one physician, one medical director of a hospital, and one high officer from a consulting company) to the absence of inspections or audits, by the tutelage, to the implementation of the detailing ceiling in the NHS istitutions, which apparently was one of the reasons for the apparent lack of generalized control of the PSRs access to physicians. The following transcription is quite unique to understand this evidence: «*Until 2014 nothing happened? No one checked? Nobody asked? No one asked? And nobody observed the Order? Then let's go jaywalking (Portugues expression: vamos à balda)! Portuguese people are like that!*» (I05).

The next evidence, apparently as one of the consequences from the previous one, is the fact that non-booked PSRs may succeed to visit doctors inside the NHS institutions. There were references to colluding between PSRs (the non-booked ask permission to the booked ones to perform visits in that day), health centers where booked PSRs have priority over the non-

booked ones, and the fact that in many HCOs there are clearly more than three PSRs per day in the health centers, and more than two PSRs per day in each hospital service.

The following transcription excerpts present relevant elements: «*The coordination of the Health Center does not even know (laughs)... PSRs are in the public zone of the Health Center. They enter with the consent of the PSRs who are marked, and those who are marked speak first with the doctors. And the doctors accept or do not accept depending on the time available*» (I04), «*Sometimes there are clearly unmarked PSRs and there is no sense on their part... and sometimes we are six, seven PSRs... theoretically they can not speak before us! But they can get in and talk to the doctors*» (I15), and «*Even without being scheduled, I can get into the great majority of the NHS institutions, I can´t get in in only 10%. In the other 90%, if I am not scheduled but I am the first one not scheduled (that is, I am PSR number four on that day) I still have access. And if I am the fifth or the sixth PST I still have access, provided I have patience, even if I have to contact the physicians outside the health center. Doctors who no longer wanted to receive PSRs can now take refuge with what is written in the Order, and those who already wanted to receive them, are still willing to receive them*» (I16).

There were several references (nine, from six sources) defending that the Order is not adjusted to the reality. One relevant argument is that different pharmaceutical companies should have a different number of visits, according to their profile, either investigation companies with many original products to promote, or smaller companies or generics companies that have fewer novelties to promote. Other argument is based on the logic that companies promoting older products should be allowed to perform a lower number of visits.

Some of the most insightful excerpts include: «*There are different situations: a company that has three products to promote and a company that has 20 products to promote. Therefore, to say that the company has six visits to promote 20 products, or a company that has six visits to promote three products, is clearly discriminating in terms of scientific capacity and in terms of the ability to transmit or disseminate products with other applications and ethically and certainly with added value*» (I05), and «*We fell into this excess, in this madness of only being able to speak to eight physicians. Who created this regulation either is mean and knows that what is being imposed will create erosion, nerves, problems, or does not know at all what is being regulated, it was invented, it seemed logical, eight doctors per day seems a pretty number. It does not make any sense. That part (of the ability to visit a maximum of eight doctors per day in the NHS) never made sense…*» (I14).

Additional insights (however with a lower number of references) include the idea that some NHS institutions – despite controlling the PSRs access – instituted some flexibility, by allowing one extra PSR per day, or accept some exceptional situations (such as when a PSR family member passes away and PSR may visit the physicians a few days after, without losing the previously scheduled visit). Another insight is that apparently no one in the NHS institutions controls whether PSRs visit up to eight doctors per day (it would be extremely difficult to monitor).

A final topic addressed the eventual reporting of misconduct, if applicable. Ten different sources (with one reference each) alleged they were not aware of any case of misconduct (including five references from physicians and four references from doctors). Conversely, we captured seven references (from six sources) where allegedly there were cases of misconduct from PSRs (excess of visits to the NHS), but with no apparent formal, serious consequence for PSRs of for the pharmaceutical companies.

The following transcription excerpt demonstrates this evidence: «*I was aware of one situation or another, in which PSRs have been called to attention... (but) there has never been, as far as I know, a drastic consequence. At best, PSRs are called to attention, or were invited to leave the HCO and behave accordingly*» (I10). Interestingly, the notion that there were cases of misconduct reported has its origin almost entirely on high officers from the pharmaceutical industry (including two officers from consulting companies and two high officers from pharmaceutical companies, suggesting, again, that they may possess a broader view of the market).

Control patterns

This topic resulted from the coding and interpretation of several contributions from the interviewees, and is focused on the identification of different approaches to the control of the detailing ceiling, in light of several perspectives. The first perspective is the **temporal evolution**, which suggests that the 2013 ceiling was more controlled in the first months after its entry into force, up to six months to one year after implementation, and after that (at around 2014/2015) the control started to become less present and effective.

This was the aspect with more references (24, from 13 sources). The following transcription excerpts add insights to this finding: «*During some time yes, it was controlled, at the beginning, in 2013/2014, but currently there is some condescendence*» (I04), «*In 2013 and in 2014 yes, there was control, but the limitations disappeared in 2015. It's a question of people*

getting adapted to it. The Order entered into force, was fresh… and then disappeared, faded-away. In 2013 and 2014 there was a reduction but in 2015 it got back to normal in relation to the number of PSRs, just like that. When it entered into force, everybody was afraid of eventual audits (…) Nobody inspected this!» (I05), «*During the transition phase, in 2013, and during one or two years, the reduction in the number of PSRs was high, but then it got diluted, the Hospital expanded the number of authorized PSRs visits, and now I don´t even know if today PSRs even have to schedule their visits, but they try to be more discrete and organized, they avoid being a group of PSRs standing there in the hospital, and have the initiative to "dilute" themselves through different hospital services*» (I08), «*At the beginning, all institutions were more concerned in not allowing more PSRs than those allowed by the Order (…) the control was made for around one year (…)*» (I13), and «*We already knew, according to the spirit of that HCO, that it would take a few months until things got loosened again*» (I14). All these references – except one, from a consultant who is in daily contact with PSRs – came from PSRs and from physicians.

The second perspective is the **region**. Ceiling control seems to be more intensive in the north and center regions (six references from five sources), clearly noted in the following transcription excerpts: «*The control is more selective in the North hospitals and health centers. Even today, a citizen does not enter São João or Santo António Hospital without ID, whereas in São José and Santa Maria Hospitals we enter there as we want and nobody asks us anything*» (I19), and «*In the center region things are more complicated, the health centers have a higher control (of the PSR activity)*» (I15). Ceiling control appears to be less intensive in the south and interior regions (nine references from seven sources), as seen in these excerpts: «*Some NHS institutions were more permissive and gave less importance to the Order, especially the hospitals in the Interior, smaller hospitals, where limitations were less visible*» (I12), and «*I remember when the Order got into force, in 2013… when we went to meetings we commented with our PSRs colleagues from the south and we got really impressed because they didn´t have any difficulty, they had free access, and we didn´t (in the North), we had to run, to hide, we were always distressed*» (I17). And the ceiling control appears to be more intensive in bigger population centers (six references from three sources), here shown in the following transcription excerpts: «*In the bigger population areas there is a higher control, there are more PSRs and the need to control*» (I13), and «*There are areas where the control is stronger, it´s more complicated, such as for instance Lisbon*» (I15). Globally, the references were originated almost entirely from PSRs (with a small number from consultants).

The third perspective is by **type of institution**. Ceiling control appears to be lower in hospitals (in comparison to health centers or USFs), as seen in the following excerpts: «*In external medical appointments PSRs were not as controlled as in other places, because these consultations were made in extrernal pavilions, where the control was less effective*» (I08), and «*In hospitals there is no control*» (I14). Ceiling control seems to be higher in USFs, mainly due to a more professionalized management, with stricter rules, where phsycians have quotas of number of patients to see and prescription budgets to observe (depending on the type of USF). This patter can be seen in the following excerpts: «*Tendentially, USFs will be more and more difficult to visit, as USFs grow, they start getting tighter rules regarding our (PSR) presence*» (I15), and «*(there is a) Higher control in USFs*» (I16). The third evidence is even more interesting and seems to be a consequence of the implementation of the 2013 ceiling: private HCOs (such as hospitals and clinics) created their own restrictions to PSRs visits, in result of the substantial increase in the number of visits in private settings, after the entry into force of the detailing ceiling in the NHS. The following excerpts help better visualize this pattern: «*During the transition phase (after 2013) we tried to increase the number of visits in physicians' private practice, but we were not able to, because private institutions raised access limitations too*» (I16), and «*There was an increase of visits to the private practice of phycisians, after 2013, a huge increase. Indeed, this started being a problem by that time, because private practice became strongly saturated (with PSRs), and private HCOs reacted, by imposing some rules too, which didn´t exist before that*» (I17). Such as with the previous topics regarding control patterns, the great majority of contributions in this scope (type of institution) were given by PSRs.

The fourth and final perspective is by **type of HCO leadership**. The political quadrant of the direction of the NHS seems to be relevant in the way it manages and controls PSRs access to their infrastructure. A certain political quadrant and /or personal personality appear to be very critic to the activity of pharmaceutical companies and their work through the PSRs and appear to either simply block the presence of PSRs, or by making it extremely difficult.

The following excerpt supports this finding: «*And then I believe there is a question of a political faction with an extremely anti-industry attitude, with some persons highly in favor of such measures (…) They are anti-industry, and try to create barriers to the emotional impact of the visits. For instance, Fernão Ferro USF only allows on PSR on Mondays, only one physician on Mondays. And then this physician shares the information the PSR shared, with his peers, during the service meeting (the information he or she finds relevant*» (I19). Ceiling

control also appears to be dependent on ACES (groups of health centers) management. This is seen in the following excerpts: «*More importante than the Order are ACES regulations, when the ACES coordinator issues regulation about the subject, sending it to the coordinators of each unit (health center). This could in fact have impact*» (I14), and «*For instance NHS HCOs in Lisbon have a higher control, in Santarém probably too, but (the control attitude) mostly depends on the ACES*» (I13).

Perception of detailing ceiling implementation on other NHS institutions

We found another pattern which we did not address when developing the script, but that appeared during the coding process: the perception of some of the interviewees about the implementation of the detailing ceiling on other institutions. Despite the reduced number of references, we highlight five references from four sources suggesting that the majority of the NHS institutions did not implement the detailing ceiling, and one reference suggesting that the ceiling was in fact implemented (but not observed) on other institutions.

2.3 – Pharmaceutical companies' reaction

This subtopic was one of the ones we had the highest curiosity with, content analysis wise. Very interestingly, the majority of contributions were originated from high officers from the pharmaceutical industry, including top pharmaceutical companies and reference consulting firms. Seven references (from seven sources) suggest that companies had no reaction, as seen in the following transcription excerpts: «*Companies adapted to new situation, basically*» (I10), and «*Our officers devalued the situation. They told us 'do not worry about it, do the work you have to do, and leave the rest with us'*» (I15). But the great majority of participants (32 references from 17 sources) suggested there was a reaction from the companies, which consisted of six main behaviors, addressed in the following paragraphs.

The **first most referred reaction** one was to increase the investment in group sessions (six references from six sources). This was a very interesting reaction with a simple logic: bring the doctors to the companies, now that the access to the NHS is more controlled. The following excerpt adds visibility to this first reaction: «*This is a bit like Darwin's law: those that can adapt are those that can survive. Naturally, companies are looking for alternatives that do not clash with the law. Nothing prevents me from picking up a group of doctors and organizing a clinical session to promote my product. I am not going against the law, I am just complementing my promotional activity. And so, somehow, it has made industry reinvent itself a little in this perspective, adapt to the new reality and look for alternative channels*» (I10).

The **second most highlighted reaction** consisted of visiting doctors in different settings (six references from five sources), such as other places where the doctor also works at and other settings (which we will further detail a few rows below). One of the most curious contributions was this one: «*Through subterfuge! They (companies) give PSR a goal to visit between 8 and 11 doctors per day. Unleash yourself! Where you have to go, the problem is yours, you have to visit them! Go to the parking lot, go to the cafe, go to the private service where the doctor also works...*» (I05).

The **third most noted reaction** appeared to be protesting (six references from five sources). One high officer from a top pharmaceutical company explained that the tutelage did not involve the industry in the discussion of the Order, and that provoked dissatisfaction among companies: «*They (companies) reacted badly! They reacted badly to what I was saying just now. First because it was not a transparent process, they were not involved in the measure, and therefore did not understand the scope. It was a somewhat disrespectful measure of the activity of a company, any private company is entitled to have a commercial activity, so at heart they establish rules of the game which are anti-commercial in terms of the activity of companies... even legally this is a gray field, isn´t it? To what extent does the Government now manage and make decisions about what is the commercial activity of the companies? So I think that instead of gaining goodwill from the industry, even to find new ways to interact with health professionals, there was even an unwillingness to collaborate. I don´t mean the industry did not collaborate, I believe there was a lot of collaboration, but I think that, as with all measures that are implemented without industry involvement, they are not well received because they have an impact on the commercial activity of companies*» (I09).

The **fourth most mentioned reaction** consisted of a higher investment in digital channels and promotion tools, such as e-mailing and webinars, due to the lower cost and easiness of access. The following excerpt explains this reaction: «*Digital has certainly grown at the expense of this Order. And so on the one hand I think we should always look at things in a positive way and realize: 'OK, we have a barrier here! How are we going to get past it?' I have to create legal alternative channels, without going against what that barrier*» (I10).

The **fifth most referred reaction** consisted of the reduction of the sales force (four references from four sources), that is, firing PSRs, but curiously two of the four references signal that these collective terminations were only partially explained by the entry into force of the Order. One interviewee even suggested that some companies used the Order as an argument to fire PSRs, who otherwise would have been fired anyway, with the Order or without it:

«*There was some concern and there were one or two companies that at the time justified the reduction of PSRs with this measure*» (I19).

The **sixth most mentioned reaction** consisted of the usage of Medical Science Liasions (MSLs), as a strategy to minimize the impact of the entry into force of the Order. Interviewee I19, a senior consultant with more than 20 years of experience in sales (including experience as a PSR), explained this reaction: «*MSLs have gained a great prominence, because PSRs can not speak off-label, but MSLs can; PSRs can not talk about products or studies not yet published, but the MSLs can; and MSLs do not count in the medical visits. So I think there was a structural change. There were companies that were very clear (multinationals): in an initiative of an MSL, a PSR can not be present, in order to avoid mixing promotional and scientific activity. But in the doctor's head this is associated*» (I19).

There was one very unique and curious insight: one PSR stated she was asked to sign a document where she declared she would not exceed the maximum allowed number of visits, «*(…) in other words to protect the company. Imagine that I go to a hospital to make unscheduled visits and I'm kicked out... the company washes its hands, you see? But on the other hand, the company asks us for a certain average of visits per day and we have to visit the doctors, so we always walk here on a tightrope*» (I17).

Tactics used by the pharmaceutical industry to adapt to the detailing ceiling

During our fieldwork, and according to our script, we asked interviewees whether pharmaceutical companies used some "tricks" (allways with the commas reference) to adapt to the detailing ceiling. The word "trick" was not well received by some of the participants, especially high officers from top companies, who preferred to use the word "tactics" instead, which does not have a negative meaning or interpretation. This topic received, in total, 99 references from 27 sources, and the most referred tactics were four, here described below.

The **first most referred tactic** was visiting physicians at their private practice (24 references from 17 sources), to keep the same number of visits as before Order 8213-B/2013, without the control of the NHS. This contribution from a high officer from APIFARMA adds visibility to this tactic: «*Companies can visit doctors in their private clinics, in their private offices, and there is no control and there is no knowledge of the NHS. At the end of the workday, after making the medical visits in the public (NHS), PSRs can still visit doctors in their private practices, this has to do with the guidance of each company and is totally legitimate. It is not measurable, it has never been calculated. But there has been some transfer from the public to*

the private, of course. PSRs take advantage of it and visit physicians in their private practices» (I12).

The **second most mentioned tactic** consisted of using mirror visits (usually referred to, in the daily jargon of the pharmaceutical industry, as Lines, or "satellite" companies). Pharmaceutical companies use Lines to multiply the number of visits their PSRs can perform to a given NHS institution. The mother company creates smaller, "virtual" companies (legal entities with VAT numbers), or uses former companies that resulted from acquisitions and mergers which were kept fiscally active, and enrolls PSRs to each of the smaller companies, which at some extent reached five or more lines. Then each company can perform six visits per year to a NHS institution *times* the number of Lines it has.

Initially, during the 2000's, companies were able to enroll PSRs to several Lines (i.e., PSR José could visit health center X today representing the mother company A, and then visit the same health center one week later representing the virtual company A1, then visit again one week later representing vritual company A2, and so on, thus multiplying the share of voice of the promoted product(s). One of the goals of Order 8213-B/2013 was to end the ability of PSRs to represent multiple Lines at once, by imposing one single registry, either at the mother company (marketing authorization holder), or at the company responsible for the lanch or promotion of the products (according to article 3, number 1). As a high officer from APIFARMA explained, PSRs did not easily accept being registered, at Infarmed, at virtual companies, afraid of losing benefits and assuming higher risks in layouts, and this led to a reduction on the number of Lines as compared to the 2000's.

These two concepts (before and after Order 8213-B/2013) are illustrated below in figures 11.5 and 11.6, in a theoretical situation where product ALFA is detailed in every Line (common product).

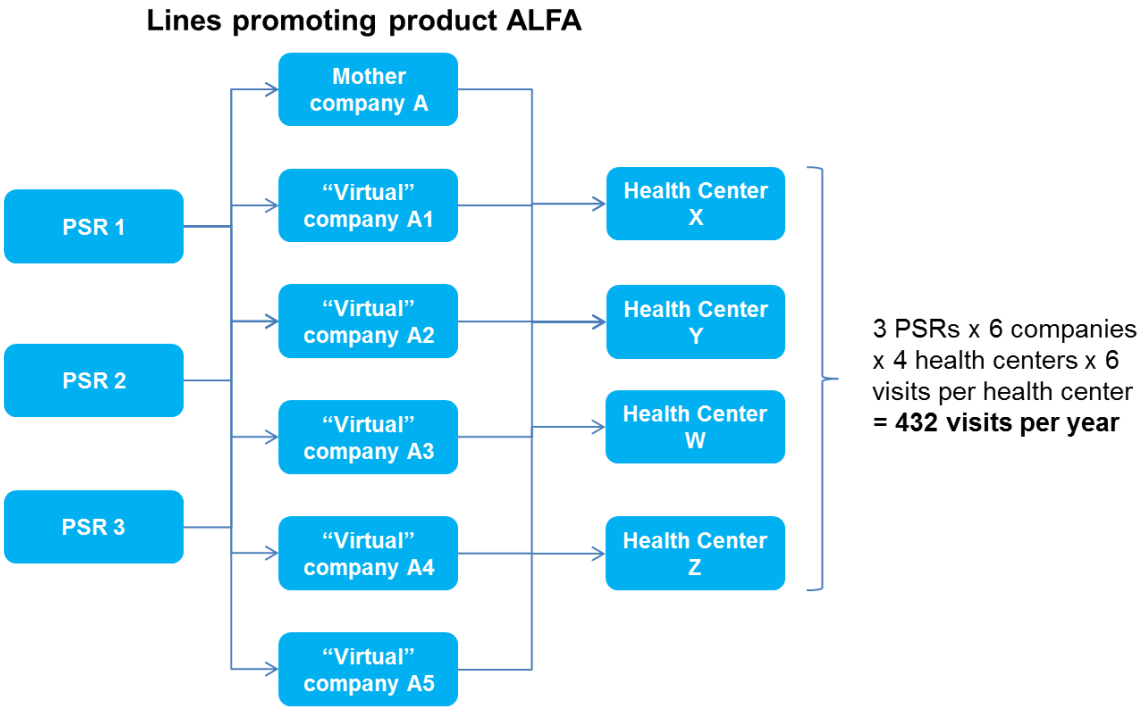


Figure 11.5 – Illustration of Lines before Order 8213-B/2013

Source: own elaboration

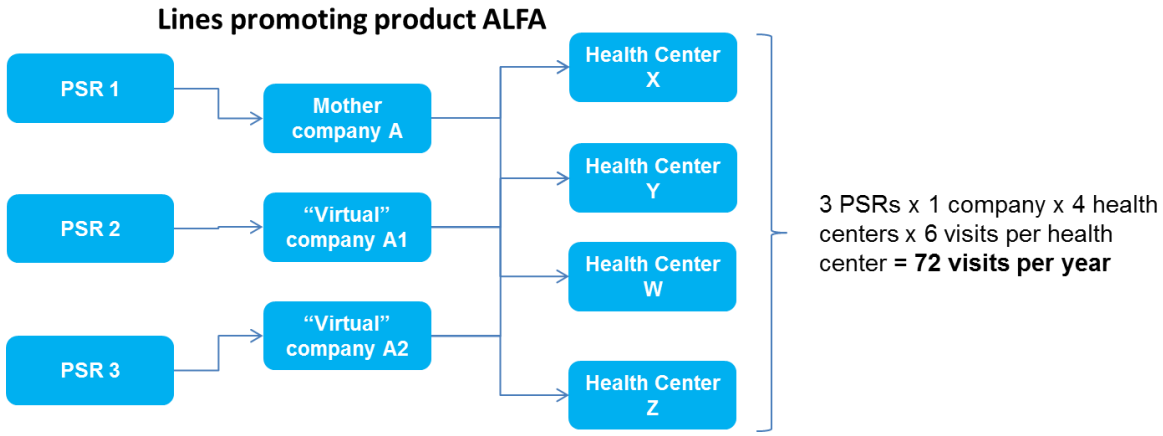


Figure 11.6 – Illustration of Lines after Order 8213-B/2013

Source: own elaboration

However, companies kept using Lines (or mirror companies) even after the entry into force of Order 8213-B/2013, now to a substantially lower extent. Typical examples of Lines: Cardiology Line, General Practice Line, Respiratory Line, and so on. Each line promotes its own products, but it is usual that each line shares one common product with the other lines, allowing the multiplication of points of contact with physicians and therefore the maximization of the share-of-voice.

Examples of insightful transcription excerpts include: «*For me, Lines are exactly the same thing. That is, I have a certain mother company X, which then has, in fiscal terms, six (smaller) companies. That is, one PSR is assigned to company X, another to company X1, with different names, but in reality they all promote... That is, it is the same thing as having a multi-bedroom house, but all rooms belong to same house and are administered precisely by the same person. Even today Lines are used. I would not say that this is 'piercing' the limit, because all this we are saying is perfectly legal. I can establish a company ABC Lda with which I will promote the product XYZ, the Infarmed validates it. All this we are talking about is an activity perfectly standardized, regulated, legal, without any problem. Bigger companies use more Lines than smaller companies, clearly*» (I10), and «*All companies have multiple Lines, but Lines do not always promote the same products. For example, I work with diabetes and my colleague works with respiratory products, with four products each, and we only have one product in common. And there are other companies that also have lines, but they do not always promote the same products*» (I15).

The **third most addressed tactic** consisted of waiting for the doctors in the parking or HCO entrance, to keep PSRs goals in terms of daily number of visits (26 references from 14 sources). The great majority of the references were originated in contributions from PSRs and from physicians. Given that some NHS institutions do control the number of visits PSRs can make per year, PSRs use this tactic to keep the share-of-voice of the products they are promoting. Some physicians revealed they even have some sympathy for the PSRs effort, by waiting hours and hours for the doctors, «*come hell or high water*» (I16). PSRs wait for the doctors early in the morning when they arrive to the HCO, or at the break time in the middle of the morning, or at lunch time, or at the end of their consultations. Additional insights are presented next, in the following transcription excerpts: «*The PSR is forbidden to go inside (the NHS institution), but nobody prevents him from being outside... in the parking lot, or near the coffee machine, nobody prevents him from being there, and he can make visits there. If the doctor smokes, he comes outside to smoke, and the PSR is there to smoke a cigarette with him... there is one visit, it counts as a visit, but it is not properly declared*» (I05), «*There are now more contacts outside the health center than inside it*» (I06), «*There were more contacts outside the Health Center, which were difficult to control by the Health Center's management*» (I07), and «*PSRs work there in the parking lot, sometimes in the rain, to have access to the doctor in that physical space that he walks from his car to the Health Center, to remind their product*» (I15).

The **fourth most mentioned tactic** is similar to the previous one, and consisted of waiting for the physicians at the bar, or at the restaurant, and speak with him or her there, during their break time. This tactic was almost totally referred by PSRs and by physicians. Examples of excerpts include: «*Doctors are people and take breaks, we can leave the Health Center, have a coffee, talk to the PSR in the cafe, and as we know each other we talk about the medicines, but without opening the computers and the leaflets. The number of contacts inside cafes increased*» (I07), and «*It's true that I also noticed... there are common areas like the bar, which we use, and at mid-morn we go to the bar, and sometimes there were PSRs at these areas, taking advantage of our presence there… they tried to get around the Order a bit*» (I08).

As the **fifth more referred tactic**, there was a very astute change in the way some pharmaceutical companies registered their PSRs' interactions with physicians. When PSRs reach the daily limit of eight visits to NHS physicians (observing the Order), further visits are classified as contacts, which can be described as informal exchanges of interaction with physicians, and therefore are not classified as normal visits. This tactic protects companies should the tutelage decide to audit CRM systems. This tactic was mentioned by three sources with a total of six references, all from PSRs. Examples of excerpts include: «*I know some companies that register the interactions as visits up to the daily threshold, and above that they register the interactions as contacts*» (I13), and «*Those are contacts, they are not visits, I can not consider them as visits. The entry into force of the Order provoked an increase in the number of contacts*» (I16).

Another tactic (**the sixth most referred one**) consisted of using back doors (or "horse doors", the Portuguese expression) to contour the control made by some NHS HCOs, which was mentioned by two PSRs and by one service director of a top hospital in the Lisbon area. The following excerpt, from a PSR, is demonstrative of this tactic: «*(…) There is always a "horse door" (back door) where the security guard does not see us. I know the Ministry of Health lives on numbers ... all right, let's say yes, (the Order) it has reached the goals ... but this is not true, because no one controls anything very much. Even in those hospitals like Santa Maria and São João, where access is more difficult, there are also "horse doors"! (laughs)*» (I17).

Two other tactics were referred, however with a low number of references: the first consists of asking permission, from scheduled PSRs, to be able to visit doctors in a given institution. A typical situation would be a non-scheduled PSR arriving to a health center, seeing three

scheduled PSRs there, and ask their permission (as a form of respect) to make his or her own visits too, after the scheduled ones finish their work; and the second, especially applied in hospitals, consists of booking visits to a specific service (for instance Cardiology) and then take the opportunity to visit phsycians in adjacent services (for instance Neurology, Internal Medicine), given that this tactic is very difficult to control.

Synthesis of the main findings – Dimension 2

The most mentioned goals of Order 8213-B/2013 were the reduction of disturbance on health care organizations (HCOs) provoked by the presence of the PSRs, the reduction of prescription and consumption (especially on newer, more expensive ones), the reduction of the commercial pressure of pharmaceutical companies on physicians, the safeguard HCPs care-related activity allowing more time for assistential tasks (such as taking care of patients, and the discipline and dignity of PSRs' access to HCPs and HCOs).

Three other goals (with fewer references) were calming public opinion stimulating the prescription of generics, and stimulating the usage of digital promotion channels. Order 8213-B/2013 preamble highlighted goals number four (safeguard HCPs care-related activity) and number five (discipline and dignify PSRs' access to HCPs and HCOs).

PSRs have to register themselves at Infarmed, and then have to book their visits at NHS HCOs, typically with administrative staff or security. On the day of the visit, access cards are given to booked PSRs, after security guards or administrative collaborators having checked whether the PSRs are booked for that day.

There were a very low number of references confirming to the full implementation of Order 8213-B/2013, suggesting it was implemented partially only, and in some cases it was not implemented at all (such as in one big hospital in the Lisbon area). According to a vast majority of interviewees, the detailing ceiling (Order 8213-B/2013) was not easy to control, and different institutions had different control approaches and not a single and unified control process (while some HCOs did not any control at all, others had a convenient interpretation of the letter of the Order, to basically almost prohibit the presence of PSRs). If by the one hand the ceiling control appears to be active in many NHS institutions, by the other hand there seems to be total absences of control of the number of physicians PSRs have contact with in each scheduled visit.

At the base of the apparent lack of control of the implementation of Order 8213-B/2013 seems to be the lack of resources (administrative, security) to fully control the ceiling, especially in smaller HCOs. Also, it appears that there were no audits made by the tutelage, which gave a certain idea of lack of control, and non-booked PSRs may succeed to visit doctors inside the NHS institutions. It appears that HCOs that control the access of PSRs admit one or more non-booked PSRs, daily. Other HCOs are strict in allowing three PSRs only, but in two shifts (three in the morning and three in the afternoon, in a total of six per day). PSRs allege they are able to enter in the vast majority of NHS HCOs, even not being scheduled.

Several interviewees declared that Order 8213-B/2013 is not adjusted to the reality, given that different pharmaceutical companies should have a different number of visits, according to their profile (investigation versus generics), size, number and type of products promoted (newer versus older). A substantial number of sources (ten) alleged they were not aware of any case of misconduct (including five references from physicians and four references from doctors), while six sources confirmed that there were cases of PSRs misconduct reported (but with no major consequence).

Order 8213-B/2013 had apparently a higher strength (in the sense of application and control) during a limited time (up to one year, according to several sources), after which the control decompressed and PSRs had a higher access to the NHS HCOs, and the perception today is that the majority of the NHS institutions did not fully implement the detailing ceiling. The control of the 2013 ceiling appeared to be more intensive in the north and center regions, in opposition to the Interior and south (Alentejo and Algarve).

Ceiling control appears to be lower in hospitals, in comparison to health centers or USFs. Likely related to the entry into force of Order 8213-B/2013 is the fact that private HCOs (such as hospitals and clinics) created their own restrictions to PSRs visits, after 2013, to combat the higher number of PSRs visiting NHS in different settings. Finally, the political quadrant of the direction of the NHS institution or region (through the ACES) appears to influence the way it manages and controls PSRs access to their infrastructure.

While a few sources suggested that pharmaceutical companies had no reaction to the entry into force of Order 8213-B/2013, the great majority of sources suggested there was a reaction from the companies, consisting of a higher investment in group sessions, increasing the

number of visits in different settings, protesting, increasing the investment in digital channels and promotion tools, reducing their sales force, and increasing the usage of MSLs.

Pharmaceutical industry appeared to use several tactics to mitigate the effect of the 2013 detailing ceiling, including visiting physicians at their private practices, using mirror visits (or Lines), waiting for the doctors in the parking or HCO entrance, or at the bar or restaurant, the registry of some of the PSRs' interactions with physicians as contacts and not as visits, and using back doors in HCOs.

We underline the contribution of a high officer from APIFARMA, summarizing the implementation and control process of pharmaceutical companies and PSRs with NHS institutions and physicians: «*Over the past 20 years, compliance with the various Orders has been gradual, as control methods have been increasing, with a shift from paper-to-digital control systems and from digital to digital units to digital network*» (I12).

This high officer then finalized with a very unique interpretation of the situation regarding this Order: there is a triangle between the tutelage, the physicians and the pharmaceutical industry, where every stakeholder seems to be relatively comfortable. First, «*The tutelage does not manifest regarding this Order*» (I12), and «*The only thing that is controlled is the registration in Infarmed*» (I12). Second, the physicians likely keep benefiting from the assistance from PSRs (if we broaden the scope to their practice practice too), and «*(…) no one compains about not being visited*» (I12). Second, pharmaceutical companies – despite having to adjust themselves after a very challenging period starting in the middle of the 2000's, and especially after 2010 -, appear to be relatively comfortable too, as «*(…) everyone has adapted to it and the medical visit continues to be made (…)*» (I12). So, according to this high officer, the pharmaceutical industry does not appear to benefit from "raising waves" regarding this Order.

11.4.2.3. Effect of the detailing ceiling to the NHS

3.1 – Effect on PSRs

We counted 34 references from 19 sources on this topic. Seven different sources (totaling nine references) suggested that the entry into force of the Order did not provoke a major impact on PSRs job or daily activity (most of these references come from PSRs), as seen in this transcription excerpt from a PSR: «*The honest answer is no, there was not (an impact),*

everything is done, maybe in other ways, but everything is done the same, the eight daily visits are performed such as before (...) The entry into force of the Order in 2013 changed rigorously nothing in my work as a PSR, nothing, in the number of visits to the NHS, in the frequency of visits, nothing» (I17).

Then we found other interesting contributions. The first effect (especially mentioned by high officers from the pharmaceutical industry, including pharmaceutical companies, APIFARMA and consulting companies, totaling 12 references from eight sources) was the higher effectiveness and efficiency of the PSRs, and therefore of the visits, as seen in the following excerpts: «*PSRs now bring news, they not only present the product in a simplistic way, but they add something, such as a study, or another situation that adds value, that is, in summary, they are now more informative*» (I08), «*From the moment there is a limitation on the number of contacts, for example, I know that if I could do 20 contacts in a year with a doctor, and now I can only do six, I have to find a strategy that allows me in those six to be as effective as possible, because I know I will not have more antenna time*» (I10), and «*Visits today are more conscientious, probably take longer, and need to have content. They have to be effective because you do not know when to go back there, visits are more effective now*» (I14).

Other effect noted by four sources (five references) was the dismissal of PSRs. Based on the contributions from the interviewees, we noted mixed interpretations about his effect. By the one hand, some participants suggest that the effect of the Order was so strong that its consequence was the drastic reduction of the number of PSRs in the market, here explained by one physician: «*There were dismissal of PSRs*» (I04). By the other hand, there are suggestions that the dismissals were a consequence of the crisis the industry had already started to suffer before the entry into force of the Order, here explained by one PSR: «*I think that, at that time, (the Order) it had an impact because it coincided with a restructuring of the industry and many PSRs were fired*» (I17).

Another effect was the fact that PSRs had to try to find and visit physicians in other settings, as addressed previously (at their private practice, at the parking, at restaurants).

One more effect appeared to be the increase in the area (or size) of the territories for each PSR. According to some interviewees, this was the reaction of companies to the reduction in the number of PSRs, where the ones that stayed had now to increase their regions – not necessarily the number of physicians to visit – and now it appears to be easier to have fully scheduled agendas. This effect was mentioned by two PSRs and one senior consultant. This

effect was explained by one PSR: «*Territories have increased in size, because once the access to health professionals has been limited by the six annual visits, some companies have either been conditioned by this or have taken advantage of this to reduce the size of the PSRs teams, because if each health professional can only receive six visits a year, some PSRs do not really have work to do on a day-to-day basis. And what was the consequence? The zones or territories have increased a lot! The specialization was reduced, for example, I used to visit hospitals only, and now I also visit General and Family Medicine (at the Health Centers / USFs). At that time I used to visit Hospital Santa Maria only and then I started to cover all Lisbon and Azores. Well, if I'm in Lisbon, I can hardly keep up with my clients in Azores!*» (I16).

Another effect on PSRs was higher compliance on the work performed (two references from two sources, both physicians). The relation with physicians is not more formatted, more compliant, there are more courses and training on ethical and deontological aspects (to which contributed the internal code of APIFARME, whose members have to comply with).

3.2 – Effect on pharmaceutical companies

The effect of Order 8213-B/2013 on pharmaceutical companies can be seen especially in two aspects: the first was an increased usage of other channels and tools to complement detailing (16 references from 10 sources), and the second was the reduction in the frequency of visits inside NHS institutions (ten references from ten sources). Regarding the first effect – apparently not entirely due to the Order but likely in part related to - companies started using more digital channels such as e-mailing, webinars, and other types of visits such as clinical meetings.

A high officer from a top pharmaceutical companies explained this tendency: «*There has been a progressive reduction in the number of PSRs in the industry, with the investments increasingly being allocated and focused on other channels, namely digital and new technologies*» (I09).

Concerning the second effect, companies increased the number of interactions of physicians outside the NHS infrastructure, such as mentioned previous in their private practice, and other settings outside the HCOs. Curiosly, there were three sources (with five references) suggesting that the total number of interactions with physicians is the same as before the entry into force of the Order, if considered the sum of visits inside the NHS HCOs and the visits and contacts outside the NHS insfrastructure. **This is one of the most important insights to**

this thesis, which may help us to understand the results obtained in the quantitative section of our research.

A contribution from a PSR allows a clear conclusion about this evidence: «*As for the effect of the Order, if we divide the total annual number of visits and contacts by the number of working days, we will get the same number as we had before the entry into force of the Order. I have fewer visits, but I also have more contacts*» (I16). There were two additional effects with a reduced number of references: companies adapted to the new reality («*I think that institutions and entities have adapted and created the mechanisms of time and space, and of the discipline of this contact, I think there was no special problem*» (I01), and companies broadened their scope to include other stakeholders to visit, such as pharmacists and other health care professionals.

This topic also addressed eventual differences in the effect of the Order depending on the size of the pharmaceutical company. Only one interviewee mentioned that the effect was equal to all companies, bigger and smaller. The great majority of participants (11 references from 10 sources) mentioned that companies more dependent on detailing and companies with higher compliance suffered more intensely, as explained by one physician (I08) and one PSR (I13): «*I think those who had the higher intensity of visits were not benefited because if they know, from their research, that detailing has an impact on sales of the product associated with a certain number of visits, then at that time maybe they have not benefited from the Order*» (I08), and «*The Order did not impact companies in the same way. Compliant companies, or companies with a higher conscience of compliance, suffered a higher impact. There are companies that do not comply, which make more than six visits per year to each institution, there is a fraction that does not comply. Companies with a higher intensity of detailing suffered more*» (I13).

Another evidence is the fact that bigger companies adapted better to the entry into force of the Order. This seems eventually incoherent with the previous evidence, but it is not, since bigger companies – typically more detaling intensive – were the ones that suffered more with the detailing ceiling, but at the same had a better capacity to adapt to it, using their bigger resources, both administrative (for all the work of registering PSRs at Infarmed) and commercial (using tactics such as the previously mentioned Lines, and by complementing their commercial endeavors with alternative channels and promotion tools).

A PSR working in the Lisbon provides additional visibility on this topic: «*Those who were already big, are still big, defended themselves better. Anyone who was already small, maybe did not defend himself so well, lost, because when you lose SOV, you lose. Whatever is born of this interpersonal relationship begins with this SOV. The more times I get there, to speak, to remind my brand, my name, everything else comes from there. So if I'm big and we're four PSRs, we visit doctors less often after the Order, but we're still four PSRs. If I was already small, and I had only one or two PSRs, I suffer more... so some companies defended themselves better than others*» (I14).

3.3 - Effect on NHS institutions

Six sources (with one reference each, from PSRs, physicians and consultants) noted that there was no major impact or no impact at all on the organization and daily activity of NHS HCOs. However, eight sources (with a total of nine references) suggested that Order 8213-B/2013 had indeed a substantial impact, by regulating and discipline PSRs access and activity in the NHS, by creating procedures for PSR enrollment, visits scheduling, and visits control. The following contributions from interviewees permit additional visibility of this effect: «*I admit there has been more regulation and regulation of this kind of interaction because, as I said, there were many complaints about the people being in a waiting room, and then seeing a gentleman come in with a briefcase, and then the gentleman arrives with the briefcase. An interesting measure could be to evaluate the number of specific complaints on this topic, whether they increased or decreased, or else to make a small panel with some ACES directors, or even hospitals*» (I01), and «*The main goal was to allow / create rules and create medical visitation schedules so that the PSRs did not stand at the doctor's door saying, 'Look, I'm here! When is it my turn?' And listen that that first there are the consultations, or first there are hospital visits, then the visit to the service, and then is the medical visit. And if I am limiting the time, if I create limitations of visits, then of course I am in some way creating rules of good procedures and speed of the daily activity of health institutions. I believe so. But it does not mean that there are no loopholes, certainly there are. But I believe that the great goal has been achieved*» (I12).

Another effect noted by four sources (two of them physicians) was a reduction in the number of PSRs and visits inside NHS institutions, and we underline the word "inside", as previously explored during this content analysis. One physicians from Algarve mentioned that «*Yes, there was a noticeable change in the Health Center, regariding the number of visits, the frequency, and the location of the contact*» (I07). Nevertheless, the number of PSRs started to

grow again recently, as noted by three sources (two physicians and one PSR), starting at around the year 2015 and registering a stronger increase in the last two years.

3.4 - Effect on NHS physicians

By the one hand, we found references of effects which seem to be aligned with some of the goals of Order 8213-B/2013: better assistential quality to patients and higher objectivity and concentration of physicians. The most mentioned one was having more time to assistential tasks with patients, with nine references from eight sources (including four physicians, one PSR and one consultant former PSR). Interviewees reasoned that less time dedicated to receiving PSRs equals more time dedicated to patients, allowing phsycians a higher productivity (number of medical consultations per day), which, by itself, may answer to some of the goals of the tutelage, as noted by a physicians working at a health center in the Lisbon region: «*Over time, the number of PSRs declined, which meant a reduction in the time spent by doctors on conversations with PSRs. And this was positive because doctors have more time for patients*» (I07).

Even a PSR accepted the detailing ceiling brought benefits to patients: «*A schedule (for PSRs' visits) was created, for the benefit of patients*» (I15). The effect of the detailing brough also higher objectivity and concentration to physicians, according to three sources (three references, from two physicians and one consultant), which seems coherent with the previous effect. One of the physicians explained: «*I think the impact (of the Order) was beneficial, because quantity is inimical to quality, and maybe we didn´t pay so much attention (to the visits), we didn´t value things so much, and now I prefer the current situation, because I can filter things better, there's no need to have a lot of people (PSRs there)*» (I08).

By the other hand, we found references to an affect that appears to be negative to physicians, which is the fact that they now receive less information and less updates on novelties (new drugs, new combinations, new studies, and so on), mentioned by five sources (with six references), including three physicians and a high officer from IQVIA. The following transcription excerpts from two physicians are quite elucidative: «*If we're talking about a product of recognized value, approved by Infarmed, if the doctor does not get to know about it because it has not been sufficiently publicized (due to the restrictions to PSRs), because doctors do not always go to university and they (the new products) have already appeared after they (doctors) left university. And if the therapeutic concepts change with the studies and the evolutions ... if there is this block to the information, there is a direct loss also for the*

National Health Service and for the benefit of the patients. Yes there is!» (I05), and «*But it was also negative because we had less information, because PSRs do not only bring us information with a commercial objective in mind, with the company goal of making money derived from a higher prescription of their product… They bring us information and we gain from it, such as being able to use a new drug, or use a drug in other domains but safely, and so I think both parts have lost, pharmaceutical companies and physicians*» (I07).

It was also very interesting to understand the perspective of the pharmaceutical companies, especially the contributions of a high officer from a top company in Portugal, here she suggested that PSRs are not the main cause for the physicians lack of productivity or conditions to work. She explained that «*(…) the bureaucracy of the health professional is so great, and has grown so much, that maybe even today it is more difficult for the doctor to exercise what is the noble activity that is seeing patients and talking to patients and diagnosing them and to treat them well, as a result of excessive bureaucratization, lack of automation, inefficiency of systems, this may turn out to be a much greater obstacle than interaction with the pharmaceutical industry, which ultimately brings structured and prepared information, assisting health professional to be a better professionals, because we also bring what the doctors need and when they need. How often do we provide doctors with medical research upon their request?! How often do we take questions to the companies, to bring the answers ... Scientific literature, additional documentation that is requested, evidence, and assistance in creating bridges with other colleagues who already have experience, organization of meetings... I mean, we ended up being a facilitator of scientific knowledge. So I do not see PSRs as a hindrance, but rather as a facilitator if you do a good job (…) The idea is that PSRs are facilitators of the work of the health professional, who help him or she to be a better professional. And I think a lot of things happened in SNS. These, indeed, made the activity difficult. And if we asked the doctors what makes their activity more difficult: it is the PSR, or it is the lack of efficiency of the system, the computers that do not work, the networks that do not work, the papers that are requested, the calls... Anyway! I am sure that the doctor would list many other things that make their work more difficult than the effect of PSRs' visits*» (I09).

We also found five sources (totaling six references, two of them from PSRs) mentioning that the entry into force of Order 8213-B/2013 did not have a substantial effect or had no effect at all on NHS phsysicians' activity. One possible explanation is that as PSRs appeared to keep

their contacts with physicians (either inside or outside the NHS infrastructure), and the effect to physicians many have not been relevant, daily activity wise.

Structural impact of Order 8213-B/2013 on physician prescription behavior

This topic was one of the most expected insights from our research, given the need to understand the results from the quantitative phase of our thesis. The great majority of the interviewees (13 sources with a total of 14 references) alleged the detailing ceiling did not have a structural change in the way physicians prescribe, and several resons were pointed out.

The first one was maintenance of prescription habits either by the physician initiative («*I prescribe with the same criteria as I used to before the ceiling*» (I06), or by influence of colleagues and HCO guidelines («*We run a lot with service meetings, with clinical case presentations, with presentations of new studies that have come out now, the possibility of one product being able to be associated with another. There are those internal meetings between us that are a complement, that is, our information does not come only from the PSRs*» (I08). The main sources of this opinion were physicians, PSRs, and high officers from the industry, including APIFARMA («*Doctors will prescribe depending on the assessment / diagnosis they make, and not on the number of PSRs visits*» (I12)).

We then found five references (five sources) suggesting that the entry into force of the 2013 detailing ceiling may have had a marginal impact, but was surely not the main influencer of the physicians prescription behavior. A contribution from a high officer from IQVIA allows a better understanding of this point: «*If I had less access to physicians, it is likely that this can contribute to the change on my prescription profile*» (I18). Interestingly, three high officers from the NHS (a hospital clinical director, a director of a group of health centers, and a former high officer from the ministry of health) suggested that the 2013 ceiling may have had a «*marginal impact*» (I01) on physician prescription behavior.

There were then five other references to an eventual structural impact on prescription behavior. Three references (two physicians and one industry consultant) mentioning that the detailing ceiling must have provoked a delay in the beginning of the prescription of novelties, the reason being that physicians do not have the same access to new studies, new presentations, new drug combinations, and new launches, as they used to have, and therefore will start prescribing later on the product launch phase (less innovators and early adopters, and more late adopters). Interviewee I04 explained that «*There may have been some delay in terms of the prescription of new drugs or new formulations... there is some loss of updating in*

terms of therapeutic novelties, so this is a negative point of having less visits (...) Maybe prescribe an innovative product later» (I04). We also found two references suggesting that the 2013 detailing ceiling contributed to a lower prescription of medicines, vision obtained from two PSRs. The first one mentioned that «*(the effect was) less prescription and less (medicines) consumption*» (I14), and the second one explained that «*By limiting the access of PSRs to the doctors, there will be a lower prescription. Often PSRs influence prescription. And by limiting PSRs' access to the doctor, he or she will prescribe less (medicines). I do not know if it is true or not, but we have commented among ourselves that this has indeed happened. Yes, there has been some change in prescription behavior*» (I15).

3.5 – Goals attained

With this topic we wanted to evaluate whether the 2013 detailing ceiling reached the tutelage goals, from two perspectives: one was the real impact on the field (that is, in NHS settings), and one was the extent to which tutelage goals may have been achieved.

In respect to the eventual impact on the field, 11 interviewees (with 12 references) mentioned that indeed the 2013 ceiling resulted in a reduction in the number of PSRs visits inside the NHS infrastructure. As noted previously, we underline the word "inside". This evidence was curiously noted mostly physicians, high officers from the pharmaceutical industry, directors of NHSs, but not by many PSRs (only one mentioned this aspect). The other four PSRs mentioned that the 2013 ceiling had no practical impact on the field, on the territories they had to cover. Interviewee I16 explained that «*I do not think there has been an impact on reducing the number of visits and contacts*» (I16), where we underline the part "visits and contacts".

Apparently, such as approached in the topic "Control patterns" above, the practical effect of the 2013 ceiling appeared to be felt during a certain period only, in the first 1 year after its entry into force (two references, from one physician in the Center region, and one PSR in the North region). There was one reference (from one physician) to an impact which was the allocation, after 2013, of a room where PSRs can speak with doctors.

Finally, there were three very interesting references from two sources (probably two of the personalities with the highest top level involvement with the health legislative and monitoring

initiatives in the last years, in Portugal), explaining us a very simple logic: if the Order entered into force, then it must have had an impact on the field. The following excerpt is very clarifying: «*If the Order entered into force, (then) it had to have impact (laughter), that question is easy to answer, the law is to be observed, as I used to say, joking with my team. If the law was observed, (then) it had to have impact*» (I01).

Finally, a very unique insight gathered during the interview with one of the high officers from APIFARMA, regarding the true effect and reach of Order 8213-B/2013: «*I do not monitor this Order, that is, I do not know if it is more observed now than in was back in 2013. Let it be in place, everyone has adapted to it and the medical visit continues to be made and no one complains about not being visited. Did I answer you?*» (I12).

In respect to the ability of Order 8213-B/2013 to reach the tutelage goals, we obtained one major evidence (with 12 references from 11 sources), and four other evidences with a lower number of references. The main insight gathered suggests that the 2013 ceiling contributed to the regulation and limitation of PSRs access to the NHS infrastructures and physicians, which had been mentioned as one of the goals the tutelage wanted to attain. It does not seem plausible however that this effect was totally felt in all the territory of Portugal and in all institutions (mainly hospitals and health centers and USFs), based on the findings we were able to gather, and therefore we can cautiously consider this goal was partially reached.

Two other goals were mentioned as attained by the tutelage: raise ethical standards in the relation between the industry (through their PSRs) and physicians, and lower the prescription of more expensive medicines. The former received two references, one from I02 and one from I02. Both contributions were very elucidative: «*It is a relationship that, being commercial, has clinical, scientific and ethical dimensions*» (I01), and «*It reached the goals of the tutelage, in the sense of ethics and a matter of change of attitude of the pharmaceutical industry itself and the doctors... I think so ... I think that was the reason. It was ethics and it was effectiveness*» (I02).

Then we detected a substantial number of references with a critical view of the effectiveness of the 2013 detailing ceiling: four sources noted that it did not reach the tutelage goals at all (three PSRs and one high officer from a pharmaceutical company), given that the tutelage allegedly does not make any endeavors to control it *(«(…) they do not control this at all!*» (I17), and that there are other channels and tactics the industry is using to mitigate the access limitations faced in some NHS institutions *(«No (laughs) I do not think it reached the tutelage*

goals, because we are Portuguese and we are really very creative (laughs), and we adjust ourselves according to the necessities we encounter. The visit in the traditional format is probably conditioned, but we continue to have other forms of access. For example, suppose I've had six visits to a doctor this year, and I need to talk to him one more time about a study that came out or a clinical case, I'll probably send him a webinar, I'll try to schedule him a contact outside of the traditional format of the visit, and I will try to discuss such a study or clinical case with him, and invite him to drink some coffee (laughs). This is the way!» (16).

And four sources (with six references) mentioned, in a somewhat ironic manner, that the tutelage is convinced the Order is being applied and control, which is not the case. These references were originated from a physician, a PSR, a high officer from a pharmaceutical company and a high officer from APIFARMA). The most relevant contributions were «*Politically they can say Yes, (it was implemented and it is controlled)*» (I09), «*The 2013 Order had the great benefit of the economic crisis, which facilitated the compliance with the Order. It is much easier for the Ministry of Health to say that it is totally observed*» (I12), and a delicious contribution from a PSR: «*They (the tutelage) might even think they succeeded, but they control nothing! Strictly nothing! Let's say yes for the tutelage to be content, but it does not strictly control anything. Even today I was in a service, in a hospital, where we were five PSRs, and not one was scheduled! Everyone came in through the 'horse door' (back door), you see? Security guards? Administrative staff? So there isn't a 'horse door'? There is always a 'horse door' where the security guard does not see us. I know the Ministry of Health lives on numbers... all right, let's say yes, the Order has reached the goals... but this is not true, because no one controls anything very much. Even in those hospitals like Santa Maria and São João, where access is more difficult, there are also 'horse doors! (laughs)*» (I17).

3.6 – Adjustments to the detailing ceiling

At the last topic of our script we wanted to understand what would interviewees do in terms of adjustments to the detailing ceiling, should they be given the authority to do so (that is, if they were the minister of health or secretary of health back in 2013). We obtained several ideas and contributions, but the one that stands out is the recognition that they would set a less restrictive limit (10 references from nine sources). And what is curious is that, in the sources (excluding the research observations made by the researcher), we only found physicians, PSRs and a hospital clinical director, what suggests that the most interested players in

detailing (PSRs on the side of the industry, because they surely want to keep their jobs, and phsycians from the side of the NHS, because they do find detailing as an important source of information, assistance, and training) are the ones defending a higher number of visits per year (eight to ten visits per year per NHS institution, instead of the current six set by Order 8213-B/2013).

Examples of ideas given by interviewees on this scope include: «*It seems the current ceiling is a little too low. These things also, when you want them very controlled, always end up escaping in another way. I have to think in a number of visits per year… once a month ... I would say 10 visits*» (I03), and «*I would be more condescending (laughs), would set a less tight limit, with more visits, at least nine a year. I think that with these restrictions we are condemning a professional career (PSRs). And indeed the preamble of this 2013 Order, in my opinion, is shameful, this is a personal opinion, that preamble is such a thing... it is shameful*» (I04).

The second most mentioned change was the involvement of stakeholders in the tutelage decision making process, to obtain opinions, reactions, being able to improve the text of the law, and communicate the rationale of setting the limits as six visits per year, per NHS institution. A high officer from a top pharmaceutical company in particular was very clear about this change: «*I would had heard more actors, heard more people, and analyzed the situation before implementing it. I would have communicated it differently. Would have found more partners and allies in what was the primary goal, because eventually this might not be a solution as well. There could be other solutions. Maybe I'd had a different strategic approach and more stakeholder involvement ... I call into question the purpose of this process. What was the original purpose?*» (I09).

Another high officer from a pharmaceutical company was aligned with this reasoning: «*Definitely yes! (laughs) I think everything in life should be done in partnership. And clearly the State here can not have... I realize the position of the State and there are many measures that maybe if I were in the Government I would also take. I think we have to look at the people who work with us from a partnership perspective. And there is a lot that the industry can do today for the State, which it is not doing*» (I10). These two high officers contributed with half of the references.

The third most referred idea was to keep the same limits, as they were set by Order 8213-B/2013, with three references from three sources, including one from a health center group

director, and one from a physician who expressed satisfaction for the organization of PSRs visits the Order allowed. The former had this very curious reaction to the question: «*I think that was great! (laugher) I tought it was great that there were not more than three PSRs per day*» (I02). Curiously, this director (doctor, by training), disclosed, on more than one occasion during the interview, the fact that she is not a big fan of pharmaceutical marketing, especially of detailing.

The fourth most mentioned idea was especially insightful to the researcher. It consists of setting different visit limits depending on several factors, including the type of products (and companies) promoted, the size of the company, and the number of products promoted. Investigation companies promoting new products or novelties would be granted a higher number of visits per year, in contrast with companies promoting older products or generics, whose need for detailing – from a scientific and physician training point of view – is less important. Another idea shared – related to this one – was to set different limits according to the pharmaceutical company size, in terms of portfolio and number of collaborators. These ideas had three sources: a high officer from a top pharmaceutical company, a physician, and a PSR.

The following transcription excerpts provide visibility on these ideas: «*I would have probably done it a little differently. I would distinguish between relevant products in which I would allow PSRs to bring useful and important information, and less relevant products where information was no longer useful. Because they cut in all, everyone! They cut in those who brought useful information, and those who only brought information about the existence of the product, just to remind the physician about the product, even if the information was not useful. (…) The companies who bring more information are the large labs, which do research and studies, and the little ones do not do that, they are just selling. In other words, I would have differentiated the access of the PSRs or the number of visits of companies with research and new products, from the others that are only interested in selling*» (I07), «*(…) the legislation should take into account the size of the pharmaceutical company, its portfolio and the number of employees*» (I09), and «*I would have mainly regulated the number of professionals that each company can have, creating a ratio appropriate to the number of medicines that the company is promoting. That would be very wise. Because having two drugs and four PSRs in each zone does not make sense, but for example having 20 drugs and two PSRs does not make sense either*» (I14).

The following ideas have a lower number of references – two or one – but still provided very relevant insights that helped us understand interviewees' reservations and contributions to an eventual better Order – should it be revised in the coming years. One of the ideas (with two references, from a physicians and a PSR) is to allow certain flexibility in the scheduling and control process. Two examples were given: first, a situation where the doctors would not be at the NHS institution (they may have gone to a training event, or missed work, or got sick), and second, a PSR whose mother had passed away. In these situations, both interviewees proposed some flexibility to allow PSRs to re-schedule their visits without losing a "credit", that is, those visits would not count as an additional visit (to the limit of six visits per year, per NHS institution).

Another idea (mentioned by a physician with coordination experience, I05) was to define a daily limit of visits only, without a year limit, which would put on the pharmaceutical companies' hand the need to organize themselves to set which PSRs from which companies would visit which NHS institutions daily. Other idea (expressed by a former PSR, now a senior consultant) was to prohibit the Lines (which was regulated with Order 8212-N/2013, but not to a prohibition extent). One interviewee – a high officer from IQVIA – stated that he would have launched the Order sooner, given that the situation needed to be regulated.

And a final idea was to change the concept of collective visits, allowing more group visits. A high officer from APIFARMA explained that «*(collective visits) are extremely important, defining very well their content, their concept, because they are the most important for knowledge and for global information to health professionals. And as there is so much the issue of visiting doctor to doctor... There could be a discussion forum with more doctors at the same time, which is good, sharing knowledge. I would have bet a lot more on those visits*» (I12).

Synthesis of the main findings – Dimension 3

The entry into force of Order 8213-B/2013 apparently did not provoke a major impact on PSRs job or daily activity, suggesting that PSRs were able to keep the number of visits (or contacts) per day, as before the 2013 detailing ceiling. However, given the fact that the access to NHS institutions and physicians was now more controlled, pharmaceutical companies had to provide their PSRs new competences, so that they could become more effective and efficient, with a more scientific approach, with more content, now that the total number of visits per year was limited.

A limited number of interviewees linked the Order to the dismissal of thousands of PSRs, but others alleged that the Order coincided with the peak of the financial and economic crisis. PSRs daily organization appeared to have changed following the entry into force of the Order, increasingly visiting, at the transition period, doctors at their private practices, and at other settings such as the HCOs parking or bar, or restaurants nearby. Likely related to the reduction to the number of PSRs – and not necessarily to the Order itself – was the expansion of PSRs territories, now covering higher areas, and the reduction in PSR specialization (targeting both primary and secondary care).

The effect of Order 8213-B/2013 was noted to impact pharmaceutical companies in two main aspects: an increased usage of other channels and tools to complement detailing (with a substantial increase on digital), and the reduction in the frequency of visits inside NHS institutions. While the first does not seem to be a direct consequence of the Order, but certainly concurrent, the second looks like a direct consequence of it.

Some sources suggested that **companies and their PSRs were able to keep the same number of visits as before the 2013 Order**, having however to be creative and meet the physicians in other settings as noted before. As underlined previously, this single insight is one of the most important evidences capturedto help us to understand the results obtained in the quantitative section. There was a consensous about the facts that companies more dependent on detailing and companies with higher compliance were more exposed to the detailing ceiling, and that bigger companies adapted better to the entry into force of the Order.

Order 8213-B/2013 appears to have helped NHS institutions to regulate and discipline PSRs access and activity inside their infrastructure by creating procedures for PSR enrollment, visits scheduling, and visits control. This likely was an important factor – alongside with the economic crisis and other events such as the INN prescription – to the reduction of the number of PSRs and visits inside NHS institutions. A substantial number of sources (six) suggested that 2013 ceiling effect on NHS institutions was at most marginal, if any.

Order 8213-B/2013 seems to have allowed physicians working at the NHS higher levels of concentration and productivity, with more time for assistential tasks with patients. The Order also appears to be linked – at least to some extent – to negative effects on NHS physicians, in the sense that they now receive less information and less updates on novelties, including new drugs and therapeutic concepts. Five sources suggested that there was no substantial effect on physicians activity.

As suggested by a great majority of sources, **Order 8213-B/2013 apparently did not provoke a structural change in physician prescription behavior, and this is another of the main conclusions of the qualitative phase of our research.** Prescription behavior changes are more likely linked to other measures – such as the INN prescription, highly formatted prescription systems, expense ceilings, and other – than to the Order itself. Conversely, a lower number of sources (five) proposed that there must have been a change in prescription behavior with the entry into force of the 2013 ceiling, likely seen in a delay in the beginning of the prescription of new medicines.

We summarized the ability of Order 8213-B/2013 to reach its goals, in table 11.3 below.

Table 11.3 – Ability of Order 8213-B/2013 to attain tutelage goals

Tutelage goals with Order 8213-B/2013	Goals	Legislative evidence (articles excerpts)	Achievement level	Evidence level	Empirical grounding
Explicit (mentioned in the preamble of Order 8213-B/2013)	**Goal 1 Safeguard HCP care-related activity (assistencial tasks)**	"(…) create the necessary conditions so that this activity does not interfere with, or in any way interfere with, the normal activity of the services, namely with regard to the provision of health care"	Partially achieved	High	The Order likely contributed to the reduction of the disturbance on NHS HCOs provoked by the presence of the PSRs, but was not likely the main factor (INN prescription, economic and finantial crisis, …)
	Goal 2 Discipline and dignify access to HCPs and HCOs	"The purpose of this Order is to establish the general rules governing the access of PSRs to NHS establishments and services and their contact with health professionals"	Partially achieved	High	Order implementation and control processes do not appear to be generalized through the entire territory of Portugal (different regions, NHS setting, and time)
Tacit (inferred from both the interpretation of the Order articles and contributions from the interviewees)	**Goal 3 Reduce medicine prescription and consumption**	**N/A**	Marginally achieved	Moderate	There might have been some delay in the beginning of the prescription of newer, more expensive medicines. The number of references was however limited
	Goal 4 Reduce commercial pressure from pharmaceutical companies	**N/A**	Partially achieved	HIgh	Order by itself presumably contributed to this goal, but was not likely the main cause (prescription by INN, economic crisis, …)
	Goal 5 Calm public opinion	**N/A**	Partially achieved	Low	The apparent link between the entry into force of the Order and an eventual reduction of the number of complaints from patients could not be made. However, a higher control of PSRs access is likely to have mitigated the occurrence of conflicts with patients
	Goal 6 Stimulate the prescription of generics	**N/A**	Not likely achieved	Low	The change in the behavior in physician prescription in relation to generics (increased penetration) behavior is likely more linked to the compulsory prescription by INN and to the economic crisis

Source: own elaboration

The majority of sources suggested that – if they had the ability to improve the Order – they would have set a less restrictive limit in the number of visits per year, to each NHS institution (a more balanced number would be eight to 10 visits per year). Also, they would have involved the stakeholders in the decision making process, to obtain opinions, reactions, and contributions, and set a different number of visits per year according to the type of company, its size, the type (investigation versus generics, newer versus older) and number of products promoted. Other suggestions include some flexibility in cases where PSRs are not able to visit physicians due to variables not linked to their work.

11.4.2.4. Paradigm shift

This was a new dimension, not present in the script, resulting from the interpretation of the content analysis of dimensions one, two and three, where we found very clear patterns. As the main insight (with 27 references from 13 sources) there is the evidence that physician prescription behavior and the very strong reduction in the number of visits and PSRs were not linked to Order 8213-B/2013 alone, suggesting the Order's impact was at best marginal, on top of many other changes the industry had been suffering.

The following transcription excerpts help us understand this topic: «*To link the reduction in the number of visits to the legislation only, I do not think it is a good conclusion, I do not know if it is a conclusion that I can draw*» (I09), «*These measures (Order) turn out to be, as Jorge Jesus would say, "peenars" (laughs). They end up being peanuts*» (I10), «*The reduction in the number of PSRs was much more provoked by the situation than by the Order*» (I14), «*So that's what I say, this was the marriage of various interests*» (I16), «*Now, I say again that I do not know if it is because of the limitation of visits, if it is due to other limitations*» (I19), and «*I do not know if the reduction in the number of visits and PSRs was directly provoked by this measure (Order), but it helped*» (I20).

We then tried to find the patterns and measure what could have explained the previous conclusion. The highest contributors to these insights, in terms of references, were pharmaceutical Industry officers, PSRs, and Consultants. We then tried to find possible evidences to help us explain the insight described above, here structured below in four topics: **legislative and regulation initiatives** (63 references from 21 sources), **market dynamics** (25 references from 14 sources), **economical and finantial conjuncture** (15 references from nine sources), and **NHS administrative ecosystem** (five references from five sources).

A highly mentioned evidence was a series of legislation initiatives from the ministry of health to control the expense with medicines, especially between 2005 and 2014. At the source of these references we found mostly consultants, PSRs, high officers from the pharmaceutical industry, and physicians. The initiatives included, according to insights from the interviеess: 1) INN compulsory prescription (23 references from 12 sources); 2) Compulsory electronic prescription (17 references from 12 sources); 3) Increased regulation of promotion initiatives (eight references from six sources); 4) Prohibition of the Lines; 5) Successive price cuts and reduction in margins; and 6) Expenditures cap. According to a substantial majority of the interviewees, the compulsory **prescription by INN** (which entered into force in 2012 with Law 11/2012, regulated by ordinance 137-A/2012) **was likely the strongest influencer of the reduction in the number of PSRs and visits to the NHS**.

Interestingly, the highest number of references (10) were originated during itnerviews with PSRs, where some of the transcription excerpts include: «*There was also the issue of INN (DCI in Portuguese), which very sincerely I believe would have been the main reason for the restructuring (dismissals) of the sales teams, because in reality if the doctor now prescribes by INN, then he or she does not need the influence of the company brand that you're behind (…) I think it was the INN decision that had a real impact on the prescribing behavior of doctors, and had much greater impact than the Order itself*» (I16), «*The impact in prescribing is mainly due to the things doctors are exposed to, with generics, having to prescribe by INN, the very tight systems (…) They weigh much more than other things*» (I17), and «*The main one, as was mentioned at the beginning, has to do with the entry of the INN (…) With the entry into force of the prescription by INN, the clear message that was passed to health professionals is that, since there was the molecule, doctors would have to prescribe by the molecule and passing that decision to the patient... (…) This Order appears more or less at the same time as the INN. And if we are reminded by then, when this INN issue was launched, it was to encourage doctors to prescribe generic drugs. And once there were many sales forces prescribing branded products (…) I think the main measure, which affected the way doctors prescribe, was the entry of the INN*» (I18).

The **second most mentioned factor** that impacted prescription behavior and the number of visits and PSRs in the NHS was the **electronic prescription and the prescription softwares** (with PSRs and high officers from the pharmaceutical industry as the main contributors in terms of references). A former high officer from the ministry of health explained that «*For me, I think the biggest impact was electronic prescription. Electronic prescription is like the*

referee video, introduces a transparency enhancing effect, and so the actors know that their footprint is getting registered. So if I have ten cardiologists in the hospital with an average prescribing standard and there is one who is an outlier, looking at that outlier I have to realize if he/she has special patients and makes a special prescription to those patients, perfectly explained or not, has the same patients as others do but has a pattern and attitude that only prescribes more expensive medications or another type of response. I think that electronic prescription in Portugal and in whole Europe is much more determinant in this aspect than a higher or lower number of PSR visits» (I01).

Several interviewees also noted that NHS prescription softwares were purposely very closed to the prescription of branded medicines (when there were generics available, of the same active principle). These limitations included several clicks to select a branded drug, several confirmation boxes ("Are you sure you want to prescribe a brand where there is a less expensive generic available?", and similar), limitations to the search of the brand drug (medicines are sorted from the lowest price to the highest price), which likely had a very important role in changing physicians prescription behavior. Some interviewees recognized that at the beginning doctors wanted to keep their prescription independence but after a few months they were beaten by fatigue or tiredeness of having to execute so many boring procedures to select branded drugs, which is clearly seen in the following transcription excerpts: «*The doctor, in order to prescribe a certain product, often has to go through 500 thousand windows, to say yes. 'But are you sure? But are you sure? And yet, do you really think that it is this product? Look there is a cheaper one!'. It was not done innocently, clearly! The great limitation often to prescription is exactly this, that is, it is the barriers and difficulties that the authorities themselves – consciously – are creating*» (I10), «*Computer systems also condition the doctor because when prescribing by INN the process is much faster than when prescribing by commercial name, so the system itself also leads the doctor to prescribe by INN*» (I15), and «*Doctors surrender more to this new way of being, prescribing more what is suggested to them by the system, by INN. Doctors today have changed their behavior a lot, even those of the old generation... they were overcome by fatigue, they were so, so pressed... And some who are even people who always had a fondness for the figure of the PSR get tired and were overcome (beaten) by fatigue*» (I14).

The **increased regulation on promotion activities – the third most mentioned topic** regarding the legislative or regulation initiatives – was also mentioned to have had an effect on the number of visits and PSRs, and this includes not only Order 8213-B/2013, but also

APIFARMA code of conduct, and the obligation of public disclosure of incentives in excess of 60€ (at INFARMED's Placotrans platform). Some excerpts where these insights appeared include: «*Obviously today we are very limited by the APIFARMA's Code of Conduct*» (I10), and «*But I do not know if these promotional or alternative events were a consequence, that is, I do not know what has contributed most to it, whether it was the limitation to the medical visit (detailing ceiling), or whether it was the rules that limited the supports to the doctors. I would say that probably what contributed most to the appearance of new promotional forms was the limit created for the support of physicians and HCOs (report obligation in Placotrans, of values above 60€)*» (I19).

Another important legislative initiative – which was incorporated in Order 8213-B/2013 – and here referred above, was the **limitation of the Lines**, which also may have provoked an impact in the number of PSRs. Interviewee I11 – a high officer from APIFARMA – adds visibility to this topic: «*This change (the detailing ceiling) and when they ceased to authorize the 'daughters' companies, or Lines, I think it was simultaneous. The contract is with the parent company. A PSR of company X (big), that goes to the line / to the virtual company... This finished and it diminished the number of visits of the pharmaceutical companies*» (I11).

The **successive cuts in prices and in margins** was also mentioned (especially by PSRs) as an important factor to explain the reduction on the number of visits and PSRs, as explained by a PSR: «*Then the profit margins also fell a lot. Even continuing to sell a lot (in quantity), there was now a smaller profit margin, and that has led to cuts (dismissal of PSRs included)*» (I17).

A final topic which was mentioned at the legislative and regulation scope was the **successive medicines expenditure caps** negotiated since the intervention of Troika (mostly referred by consultants). The cap was negotiated between APIFARMA and the NHS, and was set a two thousand million Euros of expenses per year in its first year. Should the year amount of NHS expenses with medicines be higher than that threshold, pharmaceutical companies would pay back the differential to the NHS, based on their market share. A high officer from IQVIA explained the effect of the cap on the number of PSRs: «*The State, as regulator and payer of the drug, capped the market at two thousand millions, and by capping the market companies that had no growth had to drastically reduce sales forces*» (I18).

Another highly mentioned evidence was the changes in the market dynamics, which included: 1) The generics promotion shift from physicians to pharmacists (14 references from 12 sources); 2) The power shift from physicians to pharmacists regarding off-patent

medicines (eight references from six sources); and 3) Portfolios getting older and companies with less pipeline (new drugs) in the ambulatory market (three references from two sources).

The first and second ones (mostly mentioned by consultants and high officers from the pharmaceutical industry, especially from APIFARMA), were likely a consequence of the entry into force of the prescription by INN, given that the patient has now the ability to ask for a specific brand of generics (or follow the suggestion the pharmacist gives to the patient). Pharmaceutical companies promoting generics mostly stopped visiting physicians, moving their efforts to pharmacists, which probably contributed to a very strong reduction in the number of PSRs (the logic is simple: there are more than 30 thousand active physicians in Portugal, and only approximately 2.900 pharmacies).

These changes contributed to the rise in the protagonism (and power) of the pharmacists, in terms of the attention (and support) they receive from the industry. Some of the transcription excerpts help us understand these points: «*And for example the history of generic medicines, they stopped visiting us, they now visit pharmacies*» (I04), «*And so the pharmaceutical companies, quite simply, turned their needle. 'Okay, if the decision is no longer on the doctor, then I will not promote generic drugs to the doctor, I will promote them at the pharmacy'. So today, companies that have generics are focused exclusively - there may be one exception here or another - in the pharmacy business. And so, of course, the space with the doctor is exclusively for the branded drugs*» (I10), «*There was some transfer of visits from doctors to pharmacies, namely the companies that were promoting very old products already settled in the market, and those of generics*» (I12), and «*You get to the pharmacy, the doctor may have prescribed a specific brand of generics, and the pharmacist decides to make the switch. And that's it*» (I20).

The third one was the recognition that, by the one hand, portfolios were getting older, and by the other hand, there were a very limited number of new drug lunches, which in conjunction implied the need of a substantially lower number of PSRs. In addition to this, many companies are shifting their focus to secondary care (hospital), using KAMs and MSLs in their communication with HCPs and other hospital stakeholders, instead of typical PSRs. The next transcription excerpts from one high officer from a pharmaceutical company (I10) and a consultant (I19) help us understand this: «*Companies have invested less in sales force, but I think this is also a reflection of something else. Nowadays, the portfolios of the companies themselves or at least of the main companies, nowadays ... it's an older portfolio. That is, we do not see big blockbusters these days, so naturally the way the companies are in the market*

is completely different. And the need to have more people on the ground and promote certain products is no longer so significant» (I10), and «*There was a phase – around 2013/2014, when there was no pipeline of outpatient (ambulatory) drugs, and the new pipeline is very targeted to hospital care*» (I19).

A **third evidence we were able to identify was the decisive effect of the economic and finantial conjuncture** (with high officers from APIFARMA, IQVIA and Lean Health as the main sources of references). Portuguese economy has suffered, since 2005, two main negative impacts: the first one was the 2009 international crisis, provoking a decline of 3% in the GDP in that year; the second was the impact of budget austerity measures imposed by the Troika composed by the International Monetary Fund, the European Commission and the Central European Bank, after Portugal's request for budget assistance in April 2011.

The austerity resulted in three consecutive years with negative GDP growth rates, reaching –1,8% in 2011, -4,0% in 2012 and -1,1% in 2013. The economic and finantial crisis, according to several interviewees, had a very powerful effect on pharmaceutical companies, tremendnously reducing their commercial and marketing budgets, and therefore standing out as one of the main contributors to the reduction on the number of PSRs (and therefore visits to the NHS). This effect (Troika and both Economic and Financial crises) received 15 references from nine sources), especially from hight officers from the pharmaceutical industry (pharmaceutical and consulting companies). We selected some transcription excerpts we found more relevant: «*2013 is the time of the financial crisis (…) What had an impact (on the reduction on the number of PSRs and visits) was the economic context*» (I12), «*Troika and the economic crisis in Portugal (…) these two factors have reduced the traditional channel (PSR visits) by almost 50%. At the moment it recovers a little, it is true, but in this period of five years there was a reduction of practically 50% of the traditional channel*» (I18), and «*Due to the crisis, due to the saturation of the activity itself and if you realize that SOV (share of voice) is not a growing line without end...*» (I19).

A **fourth evidence** appears in the scope of the **NHS administrative ecosystem**, mainly consisting of administrative changes especially at health familiar units (or USFs) with their expense ceilings (with PSRs as the main contributors in terms of references). These expense ceilings had been addressed by Fischer, Koch, Kostev & Stargardt (2017), where physician prescription budgets can contain pharmaceutical spending, as the most direct way of interceding in the prescribing process. Type B USFs have tight goals in terms of expenditures with medicines (and several other dimensions of goals) in order to benefit from certain

degrees of freedom, and typically are more professional managemed than traditional health centers. The number of type B USFs grew from 69 (in 2008) to 181 (in 2013), which contributed by the one hand to a higher consciousness of phsycians (more alert to prescribe less expensive options), and by the other hand to some limitations to the activity of PSRs, in the sense that a higher number of PSRs at the USFs would imply a lower performance in assistential care indicators (number of patients seen, and other), as suggested by one of the interviewees.

The following excerpts provide relevant insights on this topic: «*An USF is a healthcare unit that has a budget to operate. It works by levels. The more the USF can operate within the budget that is given to it, the more it evolves in its level, and by evolving, gains independence. And gaining independence is what? 'I give you this full glass for you to run for 1 year. And you can drink all it's left'. Therefore the USF does a self-management of costs. And that goes by what you prescribe, that has impact*» (I10), and «*Physicians are increasingly controlled in relation to health costs, their prescription, and health units, especially USFs, are now subject to cost evaluation and mandatory prescribing by INNs...*» (I16).

Synthesis of the main findings – Dimension 4

The main conclusion of the fourth dimension is the realization that Order 8213-B/2013 was not the cause of the very strong reduction in the number of PSRs (almost 50% according to a high officer from IQVIA) and visits to the NHS. At most it may have marginally contributed to this result. At the origin of this reduction was a "perfect storm" in the Portuguese pharmaceutical market, with the center of the hurricane in the period of 2010 to 2013.

The gravitational power generated by the confluence of several exogenous factors hitting the pharmaceutical companies (including the economic and financial crisis, the intervention of Troika, medicine expenditures caps, the compulsory prescription by INN, very limiting prescription softwares, changes in market dynamics and in the NHS administrative ecosystem) resulted in a clear new paradigm, pulling down the number of PSRs in an unprecedented magnitude. A high officer from APIFARMA explained that «*Order 8213-B/2013 had the great benefit of the economic crisis, which facilitated compliance with the Order. It is much easier for the Ministry of Health to say that it is all fulfilled. But upstream also the number of PSRs was reduced, due to factors external to the Order, the Order benefited from this situation, because had it not be this way I have many doubts the Order would have been completely observed*» (I12).

Figure 11.7 below is an attempt to describe, schematically, the complexity of the forces the pharmaceutical market has suffered especially in the period from 2005 to 2013.

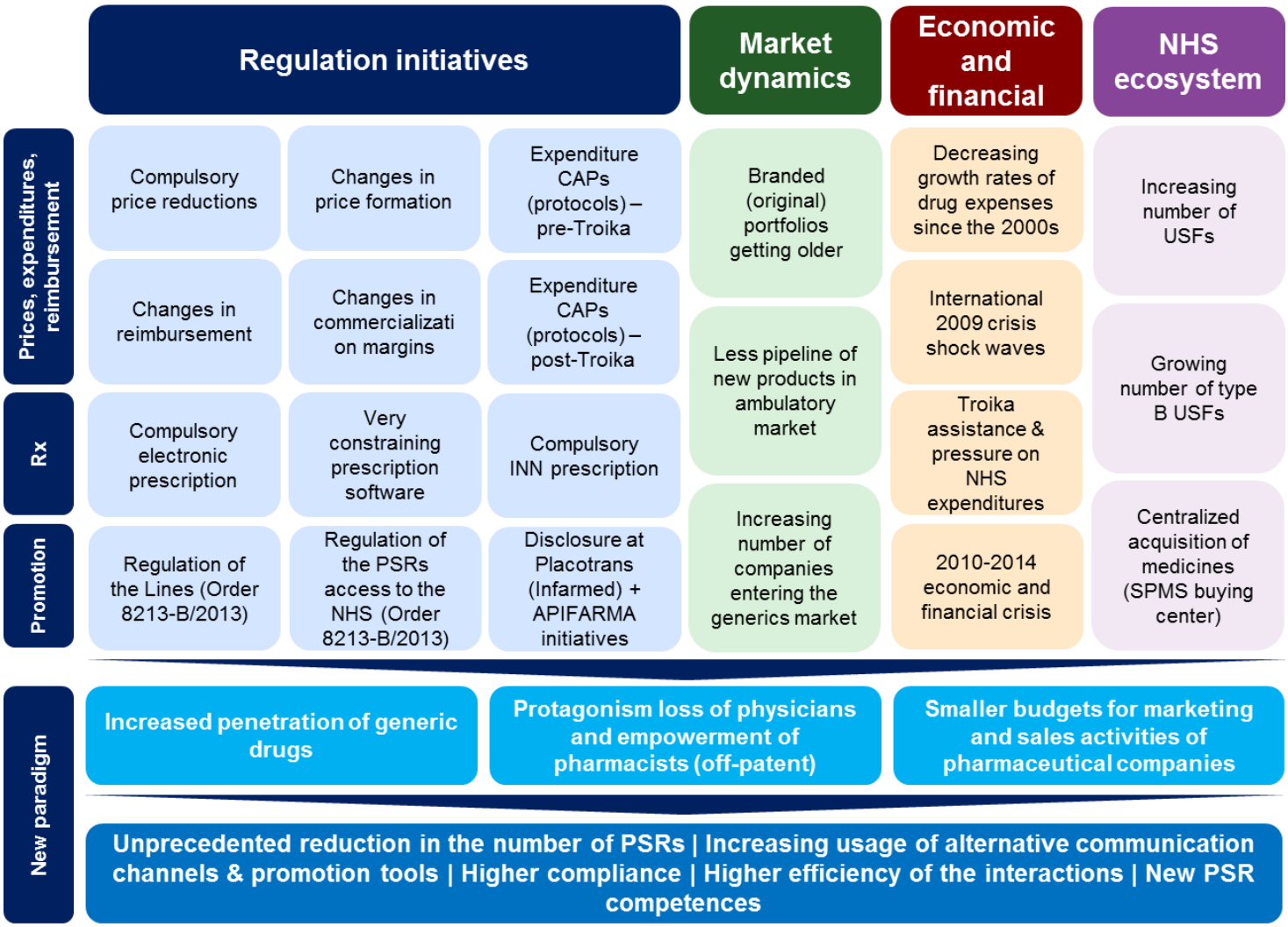


Figure 11.7 – Paradigm shift in the Portuguese pharmaceutical industry

Source: own elaboration

This paradigm shift can not only be seen in the evidences gathered from the qualitative study we developed, but also in the evolution of the expenses with medicines, incurred by the Portuguese National Health System. Historically, the industry had seen strong growths, up to

2010, period after which there was a strong medicines sales reduction, apparently aligned with a substantial increase in legislation activity. Figure 11.8 explores the evolution of published legislation and costs incurred by the NHS with medicines.

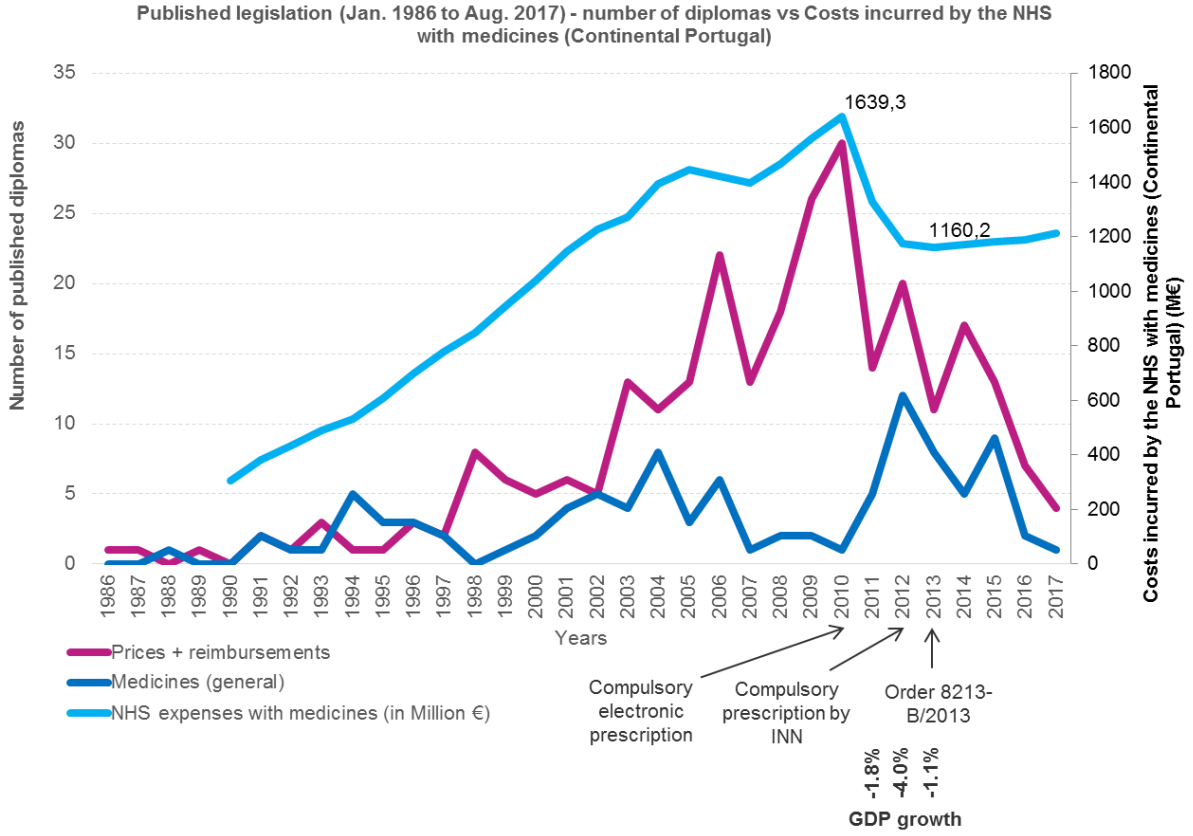


Figure 11.8 – Published legislation vs Costs incurred by the NHS with medicines

Source: PORDATA (2019) | Own elaboration

Analyzing the CAGR for five year periods (figure 11.9), we clearly see double digit growth during the nineties, then reducing to 6,8% between 2000 and 2005, then 2,5% between 2005 and 2010 (where most of the legislation activity has occurred in terms of administrative compulsory price cuts and reimbursement changes), and finally -6,3% from 2010 to 2015. If we isolate the period between 2010 and 2013, the CAGR drops to -10,9%, which resulted in a cumulative reduction of 29,2% in only three years.

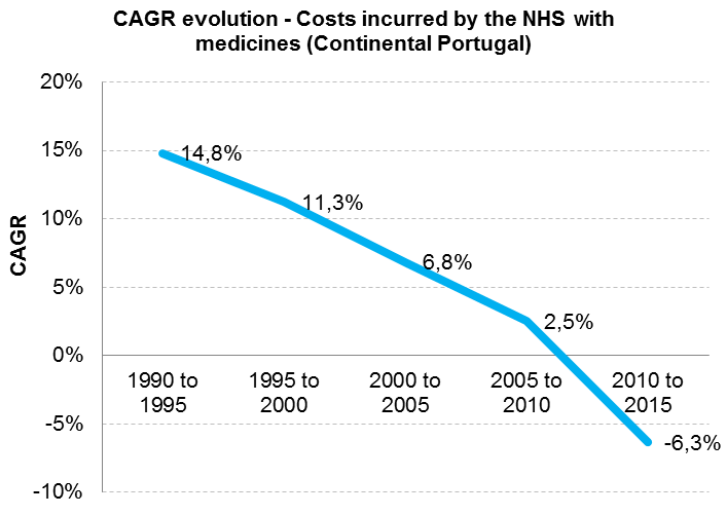


Figure 11.9 – CAGR evolution of costs incurred by the NHS with medicines (Continental Portugal)

Source: PORDATA (2019)

11.5. Conclusions

The main communication channel used to interact with physicians is still, by far, face-to-face, and the most mentioned promotion tool is detailing, apparently more valued by older than by younger physicians. Promotion instruments – especially detailing, congresses, clinical meetings and medical literature - seemingly can have a strong influence in physician prescription behavior. Detailing allows companies to maximize their SOV, explore the relation and affection between PSRs and physicians, and take advantage of the power of reciprocity. Physicians tend to value detailing given that it allows them to receive information about novelties and regular assistance from companies. PSRs competences have been evolving, with a higher scientific approach and a communication focused on the pathology and on the benefit to the patient.

Order 8213-B/2013 main goals were likely the reduction of disturbance on health care organizations, the reduction of prescription and consumption, the reduction of the commercial pressure of pharmaceutical companies on physicians, the safeguard of HCPs care-related activity allowing more time for assistential tasks, and the discipline and dignity of PSRs' access to HCPs and HCOs. Most likely, Order 8213-B/2013 was not entirely implemented on a national basis, given the difficulty to control PSRs access to the NHS in a conjuncture of reduced administrative and security staff, and with no apparent audits from the tutelage. The

visits' scheduling process does not likely observe the same procedures from NHS institution to institution, and in some cases the detailing ceiling was not implemented at all (at the date of the interviews). PSRs are able to make visits inside NHS institutions where they are not booked, where at most they will receive a reprehension, but will not likely be banned.

This 2013 ceiling had a higher effect during the first year, then losing effectiveness due to some decompression of the control. The North, Center, and high population regions apparently had a higher control than the South (Alentejo and Algarve) regions. Control is apparently higher in certain political scenarios (in ACES). Pharmaceutical companies reacted to the ceiling mainly by increasing the investment in group sessions, in digital channels and tools. Companies appeared to use several tactics to mitigate the effect of the 2013 detailing ceiling, including visiting physicians at their private practices, using mirror visits (or Lines), waiting for the doctors in the parking or HCO entrance, or at the bar or restaurant, the registry of some of the PSRs' interactions with physicians as contacts and not as visits, and using back doors in HCOs. There was already a detailing ceiling in place, in some NHS institutions, but it was not highly controlled, it was not centralized, and it did not include a maximum number of visits per year, per NHS institution.

Order 8213-B/2013 apparently did not provoke a major impact on PSRs job or daily activity. Very likely, **companies and their PSRs were able to keep the same number of visits as before the 2013 Order**. Companies more dependent on detailing and companies with higher compliance were more exposed to the detailing ceiling. The Order apparently helped some NHS institutions – the ones that implemented and control it - to regulate and discipline PSRs access and activity inside their infrastructure. Physicians working at the NHS were likely benefited in terms of concentration and productivity, with more time for assistential tasks. But physicians can suffer from the detailing ceiling by not receiving novelties and support as often as they did before 2013.

Order 8213-B/2013 apparently **did not provoke a structural change in physician prescription behavior** (at most, it may have marginally impacted the beginning of the prescription of new medicines)**.** Changes in this behavior are much more likely linked to other measures including INN prescription, highly constraining prescription systems, expense ceilings, the economic crisis, and other. Globally, the goals of the tutelage for the 2013 detailing ceiling were partially or marginally reached, only. Improvements to the detailing ceiling include a less restrictive limit, the involvement of stakeholders, and the setting of a

different number of visits per year according to the type of company, size, type of products, and number of products promoted.

Order 8213-B/2013 cannot be blamed for the strong reduction in the number of PSRs and visits to the NHS. At most, it may have had a marginal effect only, while the main contributors were a series of exogenous events that occurred especialy between 2010 and 2013, including the economic and financial crisis, the intervention of Troika, medicine expenditures caps, the compulsory prescription by INN, very constraining prescription softwares, changes in market dynamics and in the NHS administrative ecosystem, which resulted in a new paradigm, where new competences, new approaches, and new methods are needed.

When we compare the conclusions from the non-structured interviews and the ones from the in-depth interviews we have just listed, we realize that there is a very high, unexpected and very interesting proximity between both, especially regarding the effect of the the economic crisis, the Troika intervention, the INN compulsory prescription, the switch in detailing from physicians to pharmacists (in the case of generics), the very constraining compulsory electronic prescription systems (where physicians were beaten by fatigue, subordinating their prescription to price and to the options suggested by the systems), market dynamics including the shift in focus from ambulatory to the hospital market, the legislation initiatives, and a higher control of the tutelage on marketing initiatives.

11.6. Discussion (qualitative part)

As explored during the content analysis of the first dimension of our script (Pharmaceutical communication channels and promotion tools), our results are aligned with previous research on detailing and pharmaceutical marketing in general. Detailing is the main promotion tool used by pharmaceutical companies, as noted by Gagnon & Lexchin (2008), Yi, Anandalingamb & Sorrell (2003), Gagnon & Lexchin (2008), and Datta & Dave (2016), and appears to be the instrument with the highest effect on physician prescription behavior (Narayanan, Manchanda & Chintagunta, 2003; by Kremer, Bijmolt, Leeflang & Wieringa, 2008).

The main factors influencing physicians' prescription decisions include drug price and economic status of the patient (Pitt & Nel, 1988, Gönül et al, 2001; Spiller & Wymer, 2001; Stros & Lee, 2015), the quality of the product (Venkataraman & Stremersch, 2007; Fischer,

Leeflang & Verhoef, 2010; Stros & Lee, 2015), evidence & literature & guidelines (Aronson, 2006; Huskamp, Epstein & Blumenthal, 2003), the relation with PSR and the pharmaceutical company (Pitt & Nel, 1988; Stros and Lee, 2015), and own experience and habit (Pitt & Nel, 1988; and Spiller & Wymer, 2001), the physician profile (including the university he or she got the medical diploma from), peers & scientific societies, the prescription software (Spiller & Wymer, 2001; Schumock et al, 2004), trust, confidence and prestige (Pitt & Nel, 1988), adequacy to the clinical status, simplicity to the patient, and the patient him or herself.

In our research, we were able to verify that detailing is important to pharmaceutical companies because it allows them to explore reciprocity (Roughead, Harvey & Gilbert, 1998; Katz, Caplan and Merz, 2010) and use the PSRs to create friendly relations with physicians (Andaleeb and Tallman, 1996), exploring the face-to-face contact (Prosser & Walley, 2003b) to maximize the share-of-voice (Zolterns, Sinha & Lorimer, 2004; Kumar, 2015). Detailing is also important to physicians, by providing novelties (Alkhateeb & Doucette, 2008; Prosser & Walley, 2003b; Chimonas, Brennan & Rothman, 2007), remind about older products, preference for personal contact (Prosser & Walley, 2003b).

Detailing is perceived as more effective in the case of younger versus older drugs (Narayanan et al, 2003; Manchanda, Rossi & Chintagunta, 2004; Manchanda & Honka, 2005; Narayanan et al, 2005; Dave, 2013), and by our own quantitative research. Somewhat conversely to research performed by Steinman, Shlipak & McPhee (2001), our results suggest that physicians are aware and recognize the effect of detailing on their prescription behavior, but apparently are less influenced than their peers (in line with Sah & Fugh-Berman, 2013). PSRs need new competences, including the ability or sensitivity to evaluate the profile of each physician and adapt the approach and speech accordingly (Rozell & Newman, 2010; Stros & Lee, 2014), be transparent, honest, and didactic.

Our findings in the qualitative phase only partially confirm previous research on the effects of detailing ceilings. The first evidence was that the detailing ceiling may have had a marginal effect only, on the levels of detailing, while research conducted by Larkin, Ang, Avorn & Kesselheim (2014), Liu et al (2016) and Larkin et al (2017) suggested a substancial impact. Another evidence was that, with a detailing ceiling policy, the drugs with the largest detailing frequency are more exposed to the effects of the ceiling, suffering more in terms of market share, in line with previous research developed by Liu et al (2016).

11.7. Contribution to the theory

Our qualitative research also allowed several contributions to the theory on pharmaceutical marketing and drug promotion regulation, as – to the best of our knowledge – the first one to address detailing ceilings using a mixed methods approach.

The first contribution – adding to previous research conducted by Alkhateeb, Khanfar, & Clauson (2009) and Gönül & Carter (2012) on the profile of physicians more prone to detailing – is the evidence that older physicians (generally older than 45 years old) are likely more prone to receive PSRs and appreciate their regular visits, while younger physicians appear to be less dependent on detailing, using instead other information sources such as digital ones (general search engines such as Google, on-line medical communities, academic search engines, and other). Older phsycians have "grown" with the support from PSRs, are more used to receive them, and seem to be less independent in the search of scientific information (new studies, new evidence) in comparison to their younger peers.

Another contribution is the evidence that physicians appear to be aware of the effect of detailing on their prescription behavior. While Steinman, Shlipak & McPhee (2001) found that more than 60% of physicians do not consider that detailing can influence them, all our interviewed physicians (seven) recognized the influence of detailing on their prescription behavior through drug novelties, the affective component, alerting to some specificities, reminding old drugs, and clarifying doubts. We also contribute to the literature on influencers of physician prescription behavior by adding the university where physicians received their diplomas from. This was mentioned by two different sources during our research, explaining that different medical schools appear to have slightly diverse approaches regarding the prescription of some drugs.

We also provide additional insights on direct factors which appear to influence physician prescription behavior, which are the INN compulsory prescription, and the limitations of the prescription softwares when physicians try to prescribe an original drug when a generic with the same principle is available, contributing with specificities to previous research developed by Spiller & Wymer (2001) and Schumock et al (2004) on drug prescribing restriction policies. Likewise, we contribute with additional visibility on the importance of detailing to pharmaceutical companies, to physicians and to PSRs, adding relevance to this promotion instrument in the scope of pharmaceutical marketing. Moreover, we provide new insights on PSRs valued competences specifically transparency and honesty, adding to Rozell & Newman (2010) and Stros & Lee (2014) research.

Regarding drug promotion regulation, we provide unique and novel insights on a real, nationally-wide detailing ceiling implementation and supervision. Perhaps the most important ones are the evidence that without a proper and regular control, a detailing ceiling may not be taken seriously by some stakeholders in the pharmaceutical industry, and the insight that a detailing ceiling may not fully reach the goals that led to its implementation, especially on its ability to impact physician prescription behavior (which was, in our research, only mentioned in the case of newer drugs, whose beginning of prescription may be delayed with a detailing ceiling when it is controlled).

Our research also provides new insights on the difficulties on the implementation and control of a detailing ceiling from several perspectives including the NHS infrastructure, the pharmaceutical companies and their PSRs, and the physicians, as well as reactions to the ceiling from the pharmaceutical industry in general, and possible tactics pharmaceutical companies and PSRs may use to mitigate or circumvent the effect of the ceiling.

We also contribute with new theory on the effect of a detailing ceiling on physicians, on NHS institutions, on PSRs, and on pharmaceutical companies. Finally, we add new insights about a pharmaceutical market impacted by severe exogenous shocks, resulting in a paradigm shift, also helping to understand the combined effect of these shocks on the number of PSRs and detailing dynamics.

11.8. Empirical model – synthesis of the qualitative study

The qualitative empirical model (figure 11.10) was built based on the data gathered at the qualitative phase of our research (non-structured and in-depth interviews).

The qualitative empirical model incorporates not only our three initial dimensions (Pharmaceutical communication channels and promotion tools, Implementation of the detailing ceiling in the NHS, and Effect of the detailing ceiling to the NHS), but also a fourth dimension we detected during the non-structured interviews initial step and then especially during the in-depth interviews phase. The empirical model figure demonstrates the complexity of the pharmaceutical market and evidences the need to observe a broader analysis. We are convinced that the mixed methods approach fully demonstrated its scientific power in our research.

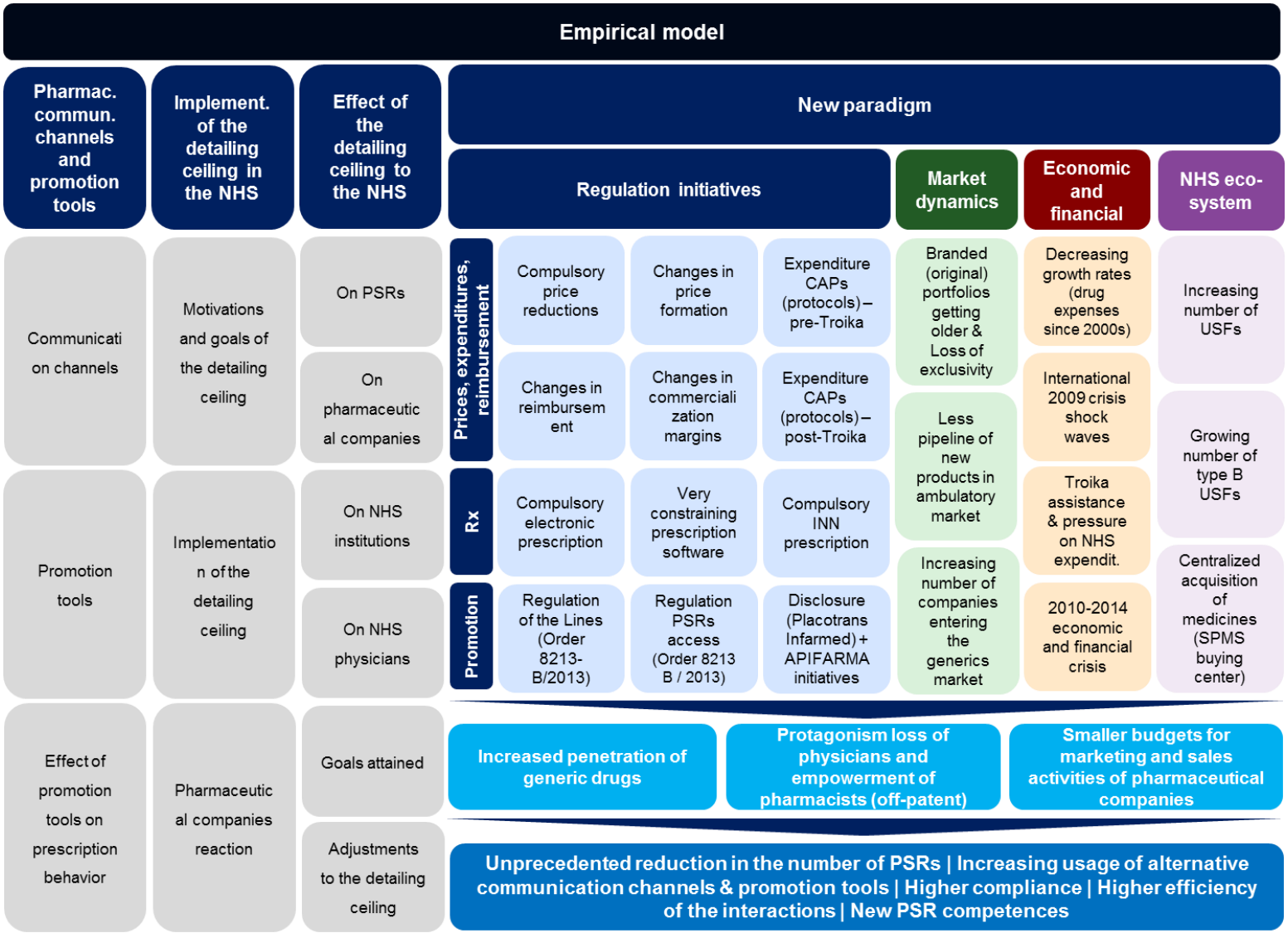


Figure 11.10 – Qualitative empirical model

In the scope of the qualitative empirical model, we also present the qualitative empirical model explanatory table, where we can find a brief definition and additional information on each of the dimensions and sub-dimensions proposed (table 11.4).

Table 11.4 - Empirical model explanatory table

Macro dimension	Unit (Sub-dimension)		Definition	Observations
Pharmaceutical communication channels and promotion tools	Communication channels		Means or vehicles through which the message moves (sender to receiver)	Most usual communication channels (face-to-face, on-line, telephone, mail) used by pharmaceutical companies to vehiculate their messages, and pattern changes in the last years
	Promotion tools		Instruments used by companies to develop interactions with clients	Main promotion tools (detailing, mailing, congresses, e-mailing, medical meetings, journal advertising, e-detailing, and other) used by pharmaceutical companies to interact with physicians, and pattern changes in the last years
	Effect of promotion tools on Rx behavior		Impact of promotion tools on physicians prescription behavior	Factors influencing physician prescription decisions | Effect of promotion tools on physician prescription behavior | Perception of detailing influence on own prescription decisions | Importance of detailing to companies and to physicians
Implementation of the detailing ceiling in the NHS	Motivations and goals of the detailing ceiling		Motivations and objectives of the tutelage for the detailing ceiling	Main motivations of the tutelage to launch the 2013 detailing ceiling
	Implementation of the detailing ceiling		Process of implementation, on the field, of the detailing ceiling	Perception of adequacy of implementation of the 2013 detailing ceiling | Perception of the effectiveness of the control (if any) made by NHS institutions | Knowledge of cases of PSRs misconduct reported and measures taken by the tutelage
	Pharmaceutical companies reaction		Reaction of the companies to face the entry into force of the detailing ceiling	Pharmaceutical companies reaction to the entry into force of the 2013 detailing ceiling, and eventual reactions to it
Effect of the detailing ceiling to the NHS	On PSRs		Effect of the detailing ceiling on PSRs activity	Effect of the 2013 detailing ceiling on daily PSRs activity (number of visits, contacts, reactions, tactics used
	On pharmaceutical companies		Effect of the detailing ceiling on companies promotion decisions	Effect of the 2013 detailing ceiling on companies decisions to allocate investments in other promotion tools
	On NHS institutions		Effect of the detailing ceiling on the activity of the NHS institutions	Effect of the detailing ceiling on NHS institutions' daily activity (productivity, concentration, organization). Effect of detailing ceiling on companies with different detailing intensity
	On NHS physicians		Effect of the detailing ceiling on the activity of NHS physicians	Effect of the detailing ceiling on NHS physicians (organization, productivity), positive and negative Existence of any structural impact on physician prescription behavior of the entry into force of the 2013 detailing ceiling
	Goals attained		Ability of the detailing ceiling to reach the tutelage goals	Perception of whether the 2013 detailing ceiling has reached the inferred tutelage goals | Practical impact on the field
	Adjustments to the detailing ceiling		Eventual adjustments to the detailing ceiling to make it more effective	Adjustments to the detailing ceiling, to make it more adequate and better to the market and NHS reality and needs
New paradigm	Regulatory initiatives	Prices	Regulation on medicines pricing	Regulatory initiatives to control and reduce medicine prices (compulsory cuts, and other)
		Prescription	Regulation on medicines prescription	Regulatory initiatives to regulate medicines prescription (electronic, INN, softwares)
		Promotion	Regulation on medicines promotion	Regulatory initiatives to regulate medicines promotion (including 2013 detailing ceiling)
	Market dynamics		Market dynamics	Influence of exogenous and endogenous variables from the market (loss of exclusivity, drug pipeline, competition)
	Economic & financial		Economic and financial constraints	Effect of the international and national crises and Troika intervention
	NHS ecosystem		NHS HCOs administrative structure	Impact of administrative changes in the structure of the NHS HCOs (growing number of USFs)

11.9. Limitations of the qualitative phase

One of the limitations of the qualitative phase is the fact that there were not young physicians in the list of interviewees, not allowing us to triangulate their opinions with the ones from senior physicians, in relation to different attitudes of younger versus older doctors about pharmaceutical marketing in general and especially about detailing. This option was taken in order to guarantee a specific profile of physician, with both public and private practice, and a substantial experience allowing physicians to comment on the evolution of detailing and pharmaceutical marketing, at least since the year 2005.

Another limitation is the fact that we were not able to interviewee very relevant stakeholders such as INFARMED and a high officer from the 19th Constitutional Government, that is, the one that launched Order 8213-B/2013. The contribution from INFARMED would have allowed us to understand, from the point of view of the controlling institution, how the processes of PSRs enrolment and registry work. We made several endeavors to obtain INFARMED's contribution, yet ended up receiving a negative response. In order to mitigate the lack of a high officer from the 19th Government, and after waiting for an answer (which did not came), we analyzed the preabule of Order 8213-B/2013.

A higher number of interviewees, especially from more regions of Portugal (including the Islands), mainly physicians, PSRs and high officers from the NHS infrastructure, would have allowed a higher representativeness. However, in order to observe very demanding timings regarding the development of this thesis and considering that we have a reasonable representation of the main stakeholders, we limited the number of interviewees to 20 (however five more interviewees than initially defined).

12. Discussion (global)

Our results globally adhere with previous theory on pharmaceutical marketing. Taking Model 7 as a reference, detailing flow effect on drug sales is consistent with previous research conducted by Kremer et al (2008), Stremersch & Van Dyck (2009), and Stremersch & Lemmens (2009). It also appears to be the promotion instrument that generates a higher effect on prescription behavior, in line with research performed by Pitt & Nel (1988), Narayanan, Desiraju & Chintagunta (2004), Narayanan, Manchanda & Chintagunta (2005), Kremer et al (2008), among others. Detailing also appears to reduce price elasticity of drugs (reduces physicians' price sensitivy) as predicted by Rizzo (1999), Gönül et al (2001), Narayanan et al (2004), and Windmeijer et al (2006). In our case, this is especially evident in the case of much younger (quartile 1) and much older (quartile 3) products. Our data also suggest that detailing evidences carry-over effects, that is, the cumulative investment of detailing has a positive effect on drug sales, as demonstrated previously by Narayanan et al (2004), Zoltners, Sinha & Lorimer (2004), Yi (2008), Montoya, Netzer & Jedidi (2010), and Liu et al (2016). In our data, the effect of detailing stock is especially strong among younger or much younger products. The theory, including Dong, Manchanda & Chintagunta (2009) and Liu et al (2016), predicts that detailing efforts performed by competitor drug brands (competitive detailing) affect own brand number of prescriptions. In our data, this was partially seen, since it only was verified in eight out of 18 products. Our data suggests that detailing efforts appear to have a higher effect on prescriptions at the initial stages of the product life cycle. This evidence is supported by previous research conducted by Narayanan et al (2003), Manchanda, Rossi & Chintagunta (2004), Manchanda & Honka (2005), Narayanan et al (2005), and Dave (2013).

Table 12.1 below shows average elasticities reached in Model 7 against expected elasticities found by Kremer et al (2008), and Leeflang & Wieringa (2008). In the second case, we used Leeflang & Wieringa (2008) results from their application of a simplified version of Wittink (2002), the one which has average elasticities available in the article. The theory, mainly Kremer et al (2008) and Stremersch & Van Dyck (2009), demonstrates that detailing elasticities depend on the therapeutic or disease classes, which was seen in our data, with four different magnitudes of elasticities in the four markets analyzed. Interestingly, Market 1 (Blood) appears to observe the pattern suggested by Kremer et al (2008), with a slightly higher elasticity than the average for all markets.

Table 12.1 also suggests that average elasticities from our Model 7 are substantially lower than the one expected by Kremer et al (2008). In the case of detailing flow, the average elasticities are approximately two thirds lower. In order to compare Advertising elasticities, we averaged the results from Journal advertising and Mailing (direct marketing), which, again, evidence much lower average elasticities versus Kremer et al (2008). The expected effect of non-US was not verified, that is, European-level elasticities are not higher than US-level ones, in our data.

Table 12.1 – Average elasticies in Model 7 vs theory

	Kremer et al (2008)		Leeflang & Wieringa (2010) application of Wittink (2002) simplified			Our research - Model 7			
	Detailing (DTP)	Advertising (DTP)	Detailing (DTP)	Mailing (direct marketing)	Journal advertising	Detailing (DTP)	Mailing (direct marketing)	Journal advertising	Average Mailing + Journal advertising
Market 1 - Blood	0,392	0,295	N/A	N/A	N/A	0,118	-0,001	0,007	0,003
Market 2 - Pancreas	N/A	N/A	N/A	N/A	N/A	0,166	0,002	0,0003	0,001
Market 3 - Heart	0,392	0,295	N/A	N/A	N/A	0,005	-0,004	0,003	-0,001
Market 4 - Liver	N/A	N/A	N/A	N/A	N/A	0,131	-0,003	0,002	-0,0004
Average	0,326	0,123	0,014	0,007	0,027	0,103	-0,001	0,002	0,001

Source: own elaboration

Our results are also in line with previous research in the field of changes in pharmaceutical policy. This is seen in the case of public reimbursement, positively impacting drug sales as suggested by Scherer (1993), in our case seen in two of the three products in Market 1 (Blood). The theory also suggests that loss of exclusivity negatively impacts drug sales (Aitken et al, 2013), which was also verified in our results for the two eligible products in Market 3 (Heart). Table 12.2 summarizes this critical analysis against the theory on pharmaceutical marketing.

Table 12.2 – Summary of the critical analysis of our results vs theory – Model 7

	Brief description	Theoretical grounding (non-exhaustive)	Demonstrated by our research?	Comment (Model 7 as a reference)
Critical analysis in light of theory on pharmaceutical marketing	The effect of detailing on brand prescriptions is significant and on average positive, but modest	(Kremer, Bijmolt, Leeflang & Wieringa, 2008; Stremersch & Van Dyck, 2009; Stremersch & Lemmens, 2009)	Yes	Especially in Market 1 (Blood), Market 2 (Pancreas), and Market 4 (Liver)
	Detailing appears to be the promotion instrument that generates a higher effect on prescription behavior	(Pitt & Nel, 1988; Narayanan, Desiraju & Chintagunta, 2004; Narayanan, Manchanda & Chintagunta, 2005; Kremer et al, 2008; Dave & Saffer, 2012)	Yes	Detailing elasticities are many times higher than Mailing and Journal advertising elasticities
	Detailing appears to reduce price elasticity of drugs (reduces physicians' price sensitivy)	(Rizzo, 1999; Gönül et al, 2001; Narayanan et al, 2004; Windmeijer et al, 2006)	Partially	6 out of 18 products, mainly in Market 3 (Heart) and Market 4 (Liver)
	Detailing seems to evidence carry-over effects (stock)	(Narayanan et al, 2004; Zoltners, Sinha & Lorimer, 2004; Yi, 2008; Montoya, Netzer & Jedidi, 2010; Liu, Gupta, Venkataraman & Liu, 2016)	Yes	14 out of 18 products evidence a positive elasticity in Detailing stock
	Detailing elasticities depend on the therapeutic or disease classes	(Kremer et al, 2008; Stremersch & Van Dyck, 2009)	Yes	Market 4 (Liver) > Market 2 (Pancreas) > Market 1 (Blood) > Market 3 (Heart) (average elasticities)
	Detailing efforts performed by competitor drug brands (competitive detailing) affect own brand number of prescriptions	(Dong, Manchanda & Chintagunta, 2009; Liu, Gupta, Venkataraman & Liu, 2016)	Partially	8 out of 18 products, mainly (5) in Market 3 (Heart)
	Detailing efforts appear to have a higher effect on prescriptions at the initial stages of the product life cycle	(Narayanan et al, 2003; Manchanda, Rossi & Chintagunta, 2004; Manchanda & Honka, 2005; Narayanan et al, 2005; Dave, 2013)	Yes	On average, younger products (less time being commercialized) evidence higher detailing flow and detailing stock elasticities. This pattern was also verified in the case of Journal advertising flow and Direct mailing flow
	Public reimbursement positively impacts drug sales	Scherer (1993)	Partially	2 of the 3 products that were subject to public reimbursement significantly increased their sales
	Loss of exclusivity negatively impacts drug sales	Aitken et al (2013)	Yes	The only two products that lost exclusivity suffered in terms of sales

Source: own elaboration

With model 8.4 we obtained what we believe may be a more calibrated and adapted model to the specificities of our research. If by the one hand Model 8.4 produced elasticity magnitudes substantially lower than the ones suggested by previous work such as Kremer et al (2008) and Leeflang & Wieringa (2008), by the other hand the percentage of signals as expected and significant (sig. < 0,05) is substantially higher than than in previous research from Leeflang & Wieringa (2008).

As seen during the analysis of the structural breaks in detailing flow elasticity, our results – contrary to what is suggested by the theory on pharmaceutical marketing (Liu et al (2016), Larkin, Ang, Avorn & Kesselheim, 2014; Larkin et al, 2017) - did not provide sufficient evidence to say that detailing elasticities were significantly different before and after the entry into force of the 2013 detailing ceiling. This conclusion is robustly backed by the fact that all 15 eligible products in our analysis evidenced the same result: no significant differences in detailing flow elasticities from period 1 to period 2. We were intrigued by these unexpected findings, which demanded further research to identify the potential explanations for this behavior in Portugal.

When analyzing detailing elasticities before and after the entry into force of the detailing ceiling in light of products with higher and lower detailing intensity, we found that 20% of the drugs with the highests detailing intensity evidenced a reduction in detailing elasticity, and 71,4% of the drugs with the lowest detailing intensity evidenced an increase in detailing elasticity, which only tangentially observes previous findings from Liu et al (2016), given that these results from our research were not statistically significant. Table 12.3 summarizes this critical analysis against the theory on pharmaceutical marketing and regulation policy.

Table 12.3 – Summary of the critical analysis of our results vs theory – Model 8.4

	Brief description	Theoretical grounding (non-exhaustive)	Demonstrated by our research?	Comment (Model 8.4 as a reference)
Critical analysis in light of theory on pharmaceutical marketing	Entry into force of a detailing ceiling may impact physician prescription behavior (measured through detailing flow elasticities)	Liu, Gupta, Venkataraman & Liu (2016)	No	The Chow (1960) test revealed that detailing elasticities before and after the entry into force of the 2013 detailing ceiling were not statistically different
	Entry into force of a detailing ceiling may have a differentiated effect on the competing drugs, depending on their previous detailing intensity		No	71,4% of drugs with the lowest detailing intensity did see an increase in their detailing flow elasticities, but this effect was not statistically significant

Source: own elaboration

Results from our qualitative phase are aligned with previous research on detailing and pharmaceutical marketing in general. Detailing is the main promotion tool used by pharmaceutical companies, as noted by Gagnon & Lexchin (2008), Yi, Anandalingamb & Sorrell (2003), Gagnon & Lexchin (2008), and Datta & Dave (2016), and appears to be the instrument with the highest effect on physician prescription behavior (Narayanan, Manchanda & Chintagunta, 2003; by Kremer, Bijmolt, Leeflang & Wieringa, 2008).

The main factors influencing physicians' prescription decisions include drug price and economic status of the patient (Pitt & Nel, 1988, Gönül et al, 2001; Spiller & Wymer, 2001; Stros & Lee, 2015), the quality of the product (Venkataraman & Stremersch, 2007; Fischer, Leeflang & Verhoef, 2010; Stros & Lee, 2015), evidence & literature & guidelines (Aronson, 2006; Huskamp, Epstein & Blumenthal, 2003), the relation with PSR and the pharmaceutical company (Pitt & Nel, 1988; Stros and Lee, 2015), and own experience and habit (Pitt & Nel, 1988; and Spiller & Wymer, 2001), the physician profile (including the university he or she got the medical diploma from), peers & scientific societies, the prescription software (Spiller & Wymer, 2001; Schumock et al, 2004), trust, confidence and prestige (Pitt & Nel, 1988), adequacy to the clinical status, simplicity to the patient, and the patient him or herself.

In our research, we were able to verify that detailing is important to pharmaceutical companies because it allows them to explore reciprocity (Roughead, Harvey & Gilbert, 1998; Katz, Caplan and Merz, 2010) and use the PSRs to create friendly relations with physicians

(Andaleeb and Tallman, 1996), exploring the face-to-face contact (Prosser & Walley, 2003b) to maximize the share-of-voice (Zolterns, Sinha & Lorimer, 2004; Kumar, 2015). Detailing is also important to physicians, by providing novelties (Alkhateeb & Doucette, 2008; Prosser & Walley, 2003b; Chimonas, Brennan & Rothman, 2007), remind about older products, preference for personal contact (Prosser & Walley, 2003b). Detailing is perceived as more effective in the case of younger versus older drugs (Narayanan et al, 2003; Manchanda, Rossi & Chintagunta, 2004; Manchanda & Honka, 2005; Narayanan et al, 2005; Dave, 2013), and by our own quantitative research. Somewhat conversely to research performed by Steinman, Shlipak & McPhee (2001), our results suggest that physicians are aware and recognize the effect of detailing on their prescription behavior, but apparently are less influenced than their peers (in line with Sah & Fugh-Berman, 2013). PSRs need new competences, including the ability or sensitivity to evaluate the profile of each physician and adapt the approach and speech accordingly (Rozell & Newman, 2010; Stros & Lee, 2014), be transparent, honest, and didactic.

Our findings in the qualitative phase only partially confirm previous research on the effects of detailing ceilings. The first evidence was that the detailing ceiling may have had a marginal effect only, on the levels of detailing, while research conducted by Larkin, Ang, Avorn & Kesselheim (2014), Liu et al (2016) and Larkin et al (2017) suggested a substancial impact. Another evidence was that, with a detailing ceiling policy, the drugs with the largest detailing frequency are more exposed to the effects of the ceiling, suffering more in terms of market share, in line with previous research developed by Liu et al (2016).

Table 12.4 summarizes the critical analysis of our results against the theory, in the qualitative part of our research.

Table 12.4 – Summary of the critical analysis of our results vs theory – Qualitative part

		Brief description	Theoretical grounding (non-exhaustive)	Demonstrated by our research?	Comment
Critical analysis in light of	Theory on pharmaceutical marketing	Detailing is the pharmaceutical promotion tool with highest total investment magnitude, used by pharmaceutical manufacturers to interact with physicians	(Yi, Anandalingamb & Sorrell, 2003; Gagnon & Lexchin, 2008; Datta & Dave, 2016)	Yes	Detailing received the highest number of references
		The effect of detailing on brand prescriptions is significant and on average positive, but modest	(Kremer, Bijmolt, Leeflang & Wieringa, 2008; Stremersch & Van Dyck, 2009; Stremersch & Lemmens, 2009)	Yes	Detailing was recognized as having na effect on prescription behavior (higher number of prescriptions of the promoted drugs)
		Detailing appears to be the promotion instrument that generates a higher effect on prescription behavior	(Pitt & Nel, 1988; Narayanan, Desiraju & Chintagunta, 2004; Kremer et al, 2008; Dave & Saffer, 2012)	Yes	Detailing had the highest number of mentions regarding as being the most effective instrument
		Detailing efforts appear to have a higher effect on prescriptions at the initial stages of the product life cycle	(Narayanan et al, 2003; Manchanda, Rossi & Chintagunta, 2004; Narayanan et al, 2005; Dave, 2013)	Yes	Detailing effectiveness was recognized as having a higher strenght in the case of new drugs
		Detailing may have a different impact on different medical specialties (specialists vs generalists)	(Chung, Kim & Park, 2017)	Partially	There were some references to the different impact of detailing on GPs and on specialists
		Gifts and meals associated with detailing may impact prescription behavior	(Katz, Caplan & Merz, 2010; Bergman, 2017; Carey, Lieber & Miller, 2017; King & Bearman, 2017)	Partially	Some references suggest that these investments may influence prescription behavior
		Pharmaceutical companies may benefit from the principle of reciprocity with their detailing initiatives with doctors	(Roughead, Harvey & Gilbert, 1998; Katz, Caplan and Merz, 2010)	Yes	Both physicians and PSRs were globally aware of the power of reciprocity and its potential impact on prescription behavior
		Recipients of the detailing activities (prescribers) do not consider themselves as influenced as their colleagues	(Steinman, Shlipak & McPhee, 2001; Sah & Fugh-Berman, 2013; Riese et al, 2015; Salmasi et al, 2016)	Partially	Some of the physicians argued that they feel less influenced than their peers regarding detailing
		Certain physician profiles and situations increment the likelihood of a more frequent interaction between physicians and PSRs	(Alkhateeb, Khanfar, & Clauson, 2009; Gönül & Carter, 2012)	Yes	Older doctors are more open to detailing activities, according to a substantial number of sources
	Theory on drug promotion regulation	Entry into force of a detailing ceiling may impact physician prescription behavior	(Liu, Gupta, Venkataraman & Liu, 2016)	Partially	Changes in prescription behavior may have (at most) marginally impacted prescription behavior
		Entry into force of a detailing ceiling may have a differentiated effect on the competing drugs, depending on their previous detailing intensity: the drug with the largest detailing stock effect and the highest detailing frequency suffers the most (market share and profit decreases)	(Liu, Gupta, Venkataraman & Liu, 2016)	Yes	The drugs with the highest detailing intensity end up suffering more with a detailing ceiling, despite the fact that they may be able to adapt their strategies better than companies with a lower detailing intensity

Source: own elaboration

13. Contributions (global)

In this topic we present, in the scope of both quantitative and qualitative phases, our research novelty and uniqueness, and our contributions to the theory, to the practice, and to policy.

13.1. Relevance and Originality

In terms of **relevance**, our research answers to several scholars in the field of pharmaceutical marketing and regulation / policy. We answer to Stremersch & Van Dyck (2009)'s suggestion for future investigation on regulation of detailing policies given scant scholarly research available, and add to Liu et al (2016) findings using real data from a national-wide detailing ceiling, and not theoretical results using counterfactual simulations. Our research also answers to Wieringa & Leeflang (2013) call for additional contributions to build empirical evidence whether the European pharmaceutical market is less or more responsive to marketing efforts than the US market.

In terms of **originality**, we also provide several novelties in the field of pharmaceutical marketing and regulation / policy. This is the first investigation of this type in Portugal -, as to the best of our knowledge the majority of the papers published so far have covered mainly the US (as seen in Wazana (2000), Kremer et al (2008), and Spurling et al (2010) reviews), and a high-income country, while Portugal is a medium-income country and may involve a different reality in terms of health infrastructure, the duration of the sales representatives' visits, the frequency of contact with physicians, the type of sales calls, and other aspects such as the specific regulation of pharmaceutical companies marketing activities. The work performed in this thesis also allows scholars to analyze the results in light of several quantitative models previously previously applied by other researchers, likewise answering to Kremer et al (2008) suggestion to analyze data from Western Europe.

Our research, by isolating the detailing investments, also provides additional insights to help clarify the apparent lack of unanimous association of detailing and physician prescription behavior, as highlighted in previous research using European databases, some of them using a macro variable of global marketing investments (sum of detailing and other marketing activities investments). Our research also adds insights to answer to Wieringa & Leeflang (2013) notes for future research, as a contribution to build empirical evidence whether the European pharmaceutical market is less or more responsive to marketing efforts than the US

market. One important novelty of our research is the calibration of previous models by adapting them to the Portuguese reality (models 8.1 to 8.4).

Our research likewise studies the effect of unique, novel variables not used in previous research, such as the effect, on physician prescription behavior, of the number of products presented during the calls, the percentage of calls where physicians declared they would increase or start prescribing the detailed product, the use of printed materials during the call, and the use of tablets during the call.

Our research also provides novelty by exploring detailing elasticities in a new class – which we called "Blood" (respecting the request made by IQVIA for anonymity of classes and products) -, comprising very expensive recent drugs that noticed a substantial growth in terms of sales, and which represents, growingly from 2011-2012, a big burden on NHS budget.

We also argue this is the first study of a pancreas-related class, to the best of our knowledge and the first work performed using a mixed method approach in the same research, to help understand the quantitative results in light of the specific market, social, economical and regulatory reality of the country and pharmaceutical industry, involving in excess of 20 participants from different stakeholders (pharmaceutical sales representatives, physicians, high officers from the NHS tutelage, NHS health care organizations, and pharmaceutical companies, physicians, and consultants).

It is also the first time the effect of a nationally implemented detailing ceiling and its impact on physician prescription behavior is measured using both quantitative and qualitative data, and the first time the implementation and control of a detailing ceiling is addressed, to the best of our knowledge.

13.2. Contribution to the theory

In terms of results, we contribute with several insights to management and marketing fields of knowledge, by confirming, by the one hand, previous research on detailing conducted by Pitt & Nel (1988), Berndt et al (1995), Narayanan et al (2003), Narayanan, Desiraju & Chintagunta (2004), Narayanan, Manchanda & Chintagunta (2005), Kalyanaram (2008), Leeflang & Wieringa (2010), among others and, by the other hand, generating new evidence e.g. a stronger impact of detailing on price elasticities of younger versus older drugs, building on research conduceted by Rizzo (1999), Gönül et al (2001), Narayanan et al (2004), and

Windmeijer et al (2006)), and the finding that detailing carry-over effect on drug sales is more intense in the case of younger drugs, building on previous work from Narayanan et al (2004), Zoltners, Sinha & Lorimer (2004), Yi (2008), Montoya, Netzer & Jedidi (2010), and Liu et al (2016).

Our research also contributed by studying novel, fresh data in the study of pharmaceutical marketing and specifically detailing, as demonstrated by the deep analysis of the models, variables and conclusions of more than 40 quantitative papers in pharmaceutical marketing involving detailing. These variables are new, launched by IMS Health in the second decade of 2000, therefore with little time for analysis by previous researchers. These new variables build on previous research developed by authors such as Pitt & Nel (1988), Berndt et al (1995), Narayanan et al (2003), Narayanan, Desiraju & Chintagunta (2004), Narayanan, Manchanda & Chintagunta (2005), Kalyanaram (2008), Kremer et al (2008), Kalyanaram (2009), Dave & Saffer (2012), and many other in the field of pharmaceutical marketing.

Our research also contributed with the discovery of the inexistence of a significant statistical effect of the detailing ceiling on physician prescription behavior, which goes against previous theory developed by Brotzman & Mark (1992), Brotzman & Mark (1993), Liu et al (2016), Karas et al (2016), and Larkin et al (2017). By analyzing this effect using also qualitative research we help the academy to discover the limited reach of 2013 detailing ceiling, with insights from multiple stakeholders on the process of implementation, control, impact and improvement of a detailing ceiling. This also builds on previous research conducted by Campo et al (2006), Chimonas, Brennan & Rothman (2007), Prosser & Walley (2013a), Prosser & Walley (2013b), Grundy, Bero & Malone (2016), Skandrani & Sghaier (2016), and Saavedra, O'Connor & Fugh-Berman (2017), which studied detailing using qualitative research, but not addressing however detailing ceilings.

Our research evidenced the limited or non-existent effect of a detailing ceiling in the apparent absence of a central, firm and regular monitoring of the number of PSRs and visits, in the scope of the almost impossibility to block PSRs' access to NHS physicians in alternative settings (parking, bar, restaurant, private practice, phone, and other). This evidence is particularly relevant by building on previous research by Liu et al (2016), Karas et al (2016), and Larkin et al (2017).

Our research evidenced that the detailing ceiling benefited from several exogenous variables impacting much more the number of PSRs and physicians' prescription behavior than the

ceiling itself, again contributing with relevant and unique specificities to research conducted by Liu et al (2016), Karas et al (2016), and Larkin et al (2017). Finally, our research allowed the detection of two very different profiles of physicians, in relation to their attitude towards detailing and pharmaceutical marketing in general, thus building on research developed by Alkhateeb, Khanfar, & Clauson (2009) and Gönül & Carter (2012).

The following tables condense the contributions to the theory allowed by our research: table 13.1 summarizes the main evidences and contribution of our research to the theory on pharmaceutical marketing, generated from our Model 7; table 13.2 reviews the main evidences and contribution of our research to the theory on pharmaceutical marketing, from our Model 8.4; and table 13.3 recaps the main evidences and contribution of our qualitative research to the theory on pharmaceutical marketing and on drug promotion regulation.

Table 13.1 – Summary of the contributions to the theory – Model 7

	Brief description	Demonstrated by our research?	Comment (Model 7 as a reference)
Contribution to the theory	Detailing appears to reduce price elasticity of older drugs more intensely than of younger drugs	Yes	We reached this conclusion by analyzing the average elasticities of younger and older drugs
	Detailing carry-over effect on drug sales is more intense in the case of younger drugs	Yes	We reached this conclusion by analyzing the average coefficients of younger and older drugs
	The use of tablets (such as iPads or equivalent) during the call appear to have, on average, a positive effect on drug sales, especially of older drugs. Laptop-based materials appear to have an average negative effect on drug sales, but a positive effect on older drugs	Yes	We reached this conclusion by analyzing the average coefficients of younger and older drugs
	The use of printed material during the calls does not appear to have a substantial impact on drug sales	Yes	We reached this conclusion by analyzing the average coefficients of younger and older drugs
	Higher declared intention of starting prescribing or increasing prescriptions of the detailed product appear to be positively associated with drug sales, but only for older products	Yes	We reached this conclusion by analyzing the average coefficients of younger and older drugs
	The average number of products presented during the calls negatively impacts drug sales of the product analyzed	Yes	The higher the number of products presented in addition to the product being analyzed, the lower the sales of that product

Source: own elaboration

Table 13.2 – Summary of the contributions to the theory – Model 8.4

	Brief description	Demonstrated by our research?	Comment (Model 8.4 as a reference)
Contribution to the theory	Not all detailing ceilings may impact physician prescription behavior	Yes	Detailing elasticities before and after the entry into force of the 2013 detailing ceiling were not statistically different
	Entry into force of a detailing ceiling may not have a differentiated effect on the competing drugs, depending on their previous detailing intensity	Yes	The differences in drug elasticities of high and low intensity detailed drugs were not statistically significant (sig = 0,05)

Source: own elaboration

Table 13.3 – Summary of the contributions to the theory – qualitative part

		Brief description	Demonstrated by our research?	Comment
Contribution to the theory	On pharmaceutical marketing	Older physicians are more prone to receive PSRs and appreciate their regular visits, than younger physicians (which are less dependent on detailing)	Yes	Several references suggesting that older physicians are more dependent on detailing and the benefits they receive in terms of information and support
		Physicians appear to be aware of the effect of detailing on their prescription behavior	Yes	Our interviewed physicians recognized the influence of detailing on their prescription practice
		The University the physician got their medical diploma from may influence physician future practice as a doctor	Yes	Different medical schools appear to have slightly diverse approaches regarding the prescription of some drugs, and this passes to the medical students
		The difficulties proposedly created by NHS software on the prescription of original drugs when generics are available substantilly impact prescription behavior	Yes	Doctors appear to be overcome by fatigue when trying to prescribe original and more expensive drugs when generics with the same principle are available
		Detailing appears to be valued by physicians, pharmaceutical companies, and PSRs	Yes	The importance of detailing to several stakeholders was highly mentioned in our research
		PSRs need to have several competences, especially transparency and honesty	Yes	Transparency and honesty were mentioned as critical competences PSRs must have, adding to previous studied competences
	On drug promotion regulation	Entry into force of a detailing ceiling may impact physician prescription behavior	Partially	The detailing ceiling may delay the beggining of prescription of newer drugs
		Entry into force of a detailing ceiling may have a differentiated effect on the competing drugs, depending on their previous detailing intensity	Yes	High intensity detailed drugs will probably suffer more with the entry into force of a detailing ceiling
		Without a proper and regular control, a detailing ceiling may not be taken seriously by some stakeholders in the pharmaceutical industry	Yes	Some NHS institutions did not implement and control the detailing ceiling, and the ones who did reduced the control pressure one year after implementation
		Several stakeholders (NHS institutions, NHS physicians, pharmaceutical companies, and PSRs) face unique challenges and effects from a detailing ceiling	Yes	Multiple stakeholders can be positively and negatively impacted by the entry into force of a detailing ceiling
		A detailing ceiling may originate reactions and tactics from pharmaceutical companies and PSRs to mitigate its effectiveness	Yes	A series of reactions and tactics were developed by companies and PSRs in order to mitigate the impact of the ceiling
		The effect of a detailing ceiling may be small next to the impact of other types of regulation initiatives and exogenous shocks	Yes	The complexity of the economic, financial, regulatory and administrative context may have a much stronger effect on the number of PSRs and detailing magnitude than a detailing ceiling

Source: own elaboration

13.3. Contribution to the industry practice

Our research also contributes to the practice, considering several stakeholders scopes. The first one is regarding pharmaceutical companies, through a series of reasons. It allows a better understanding of the effect of several promotion tools (including detailing) on physician prescription behavior, using a European database, which can assist marketing and sales officers in their decisions to select the most effective promotion instruments and optimize their magnitude. These insights are therefore of decisive importance to generate a higher understanding of sales force effectiveness and its implications for sizing, targeting, and call planning strategy in pharmaceutical companies.

Companies can also benefit from the analysis of the effect of a nationally implemented detailing ceiling on the signal and magnitude of the association between detailing and prescription behavior, adjust their tactics in light of these results, and more effectively prepare eventual changes in future updates in Order 8213-B/2013.

Marketing departments from pharmaceutical companies can benefit too from the analysis of results from both quantitative and qualitative phases, with insights that may assist the communication and promotion activities, in order to meet stakeholders' (especially prescribers) expectations. The new variables used in our research provide critical insights for pharmaceutical and biotechnological companies in the scope of promotion and salesforce effectiveness.

By understanding the impact of using tables (ipads or similar) during calls, versus providing printed information or laptop-based information, companies can more easily plan and organize their detailing efforts.

By monitoring the doctors' intention of increasing the prescription of the promoted drugs, companies can more easily build an early warning system, to signal potential issues with their current detailing tactics. Companies can also be more aware of the necessity of balancing the number of products promoted during the calls, since the higher the number of other products promoted, the lower the sales of the promoted product, which is critical in terms of the efficiency of the salesteam (PSRs).

Associative institutions – such as APIFARMA – can benefit from the insights generated in our research, allowing them to be better prepared and backed by empirical evidence on the areas where the detailing ceiling may be improved, in the scope of future negotiations with the tutelage – and several suggestions and ideas were generated from our research.

Physicians – the sole stakeholder with the authority to prescribe in Portugal - can benefit too from our research, by confirming the existence, in several products analyzed, of a clear effect of detailing on prescription behavior, allowing doctors to become aware of this influence and be better equipped to interact with PSRs and the pharmaceutical industry in general. Physician chambers and associations can have a stronger intervention along with their members, through specific training or information initiatives to raise awareness on this effect.

We believe other stakeholders may find our research useful from a practice point of view. Pharmaceutical sales representatives can benefit from our research, by confirming their influence on prescription behavior, and obtaining unique insights on the new competences needed to provide physicians what they need and meet their expectations.

Pharmacists and pharmacists' chamber may have interest in the results of this research, since pharmacies would theoretically obtain financial benefits should the assumptions of higher detailing being associated with higher number of prescriptions be applicable in Portugal – which was confirmed by our research -, and in this scenario, considering an economical point of view only, higher medication consumption represents higher revenues to the pharmacy.

Another stakeholder that may interested in our research is the Health insurance private sector, as a higher number of more expensive drugs prescribed may imply a higher cost to be reimbursed to patients, meaning a higher cost borne by insurance companies. Finally, patients and patients' associations may benefit from our research, helping them become more aware of the instruments used by pharmaceutical companies to interact with physicians, and its effect on physician prescription behavior.

13.4. Contribution to the public policy

Policy makers may benefit from our research by a series of reasons. The first is the realization that detailing initiatives do impact physician prescription behavior in Portugal, especially in the case of more recent (and typically more expensive, and reimbursed) drugs.

This evidence may raise the attention on the topic of pharmaceutical marketing in general, in a scenario of very constrained budgeted costs with medicines, and also considering the opportunity costs to the public health, induced by the time doctors spend receiving PSRs at their NHS professional practice. The tutelage also can realize the extent to which Order 8213-N/2013 reached the goals described in its preamble and other inferred goals such as its effect on prescription behavior and medicines consumption, and whether the implemented cap was adequate or needs an update.

The tutelage can also understand that the ceiling may have not been totally implemented and controlled, allowing the study and launch of eventual corrective measures, incorporating suggestions to improve the ceiling in a future regulatory initiative. At the same time, the tutelage may also realize the importance of detailing and other promotion and information instruments used by pharmaceutical companies, complementing the apparently very limited physician training sponsored by the ministry of health.

Therefore, the tutelage can clearly benefit from analyzing the delicate equilibrium between the need to regulate PSRs' access to physicians and NHS HCOs, and the need to continue benefiting from the pharmaceutical companies assistance in training, raising awareness on pathologies, and assisting doctors on a regular base. Finally, based in our research the tutelage can evaluate the pertinence of introducing or reinforcing pharmaceutical marketing modules or training in medical courses, raising awareness, among medical students, of the effect of pharmaceutical marketing (especially detailing) on physician prescription behavior, and consequently on the evolution of NHS and out-of-pocket expenditures with reimbursed medicines.

14. Answer to the research question

We recall our research question:

- *What is the impact of a detailing restriction policy on physicians' prescription behavior?*

Making the bridge now with our conceptual model, our research did not confirm the results expected by previous work by Liu et al (2016), by not finding quantitative evidence to confirm the existence of changes in detailing flow elasticities before and after the entry into force of the 2013 detailing ceiling. This is backed by the fact that all eligible products (15) did not evidence a significant change in their detailing flow coefficients, using a series break-test (Chow, 1960). By other words, and making the bridge with our research variables, the entry into force of the policy measure consisting of a detailing ceiling (moderating variable) did not provoke statistically significant changes in the elasticities of the detailing intensity (measured as Ln Detailing flow), as previous literature supported.

Therefore, in the quantitative phase we were also not able to conclude whether products with different detailing intensities are impacted differently by a detailing ceiling, on their detailing elasticities.

The qualitative phase helped us to shed some light on the results of the quantitative phase, by providing insights facilitating the understanding of the impact of several exogenous variables that probably may have mitigated and diluted the potential effect of the detailing ceiling. The qualitative phase results suggested that, at most, the detailing ceiling may have potentially delayed, for a small period of time, the beginning of the prescription of newer, more expensive drugs, but as a general insight there is strong evidence to suggest that physician prescription behavior (analyzed in drug sales) may have not be considerably impacted by the 2013 detailing ceiling.

15. Conclusions (global)

As explored during the literature review phase, pharmaceutical companies' R&D investment in the development of new therapies reaches millions of dollars each year, and only a small number of new drugs are approved for human usage. In order to disseminate information about new and current drugs to prescribers – including dosage, studies, and side effects information – pharmaceutical companies develop marketing activities targeted mainly to physicians – the main prescribing class -, with instruments such as detailing, e-detailing, medical meetings, congresses, continuous medical education programs, gifts and meals, and other instruments and initiatives.

While pharmaceutical companies' representative associations engage into efforts to demonstrate the positive effects of pharmaceutical marketing and detailing on physicians education and overall public welfare, the scientific community has been demonstrating, in most articles, a relevant association between marketing initiatives and prescription behavior, with some positive and negative aspects, evidencing an association between different levels of this promotion instrument and physician prescription behaviors and attitudes.

As a general conclusion, higher intensity of detailing appears to be associated with a higher number of prescriptions of the promoted drugs - selective demand effects, where a drug is preferred over other alternative drugs, but not to higher number of prescriptions in the drug category, suggesting a prescription switch from other drugs to the promoted ones.

While it is understandable and legitimate that pharmaceutical companies have interest in improving the effectiveness of detailing and other marketing initiatives to reach a higher share-of-voice, market share and revenues using optimal combinations of marketing and salesforce investments, the discussion spills to other pharmaceutical stakeholders especially to policy makers, given that pharmaceutical marketing and particularly detailing might, on the one hand, impact spending on drugs and therefore potentially increase the burden with medicines expenditures, and negatively influence, on the other hand, physicians' available time allocated to patients' assistencial care.

Several countries have initiated policy measures to regulate the burden with medicines, including manufacturer price regulation, regulation on physician prescription budgets, patient payment policies, regulation of direct-to-consumer advertising, and regulation of marketing efforts to physicians. In the scope of this last topic, some countries have started to define

limits to the number of visits (calls to physicians) a pharmaceutical sales representative can make per day, including the United Kingdom, Spain and Portugal.

Since there is scant research on the impact of detailing restriction policies on prescription behavior, our work offers a contribution to pharmaceutical marketing and regulation policy using a mixed method approach, conducted using Portuguese data, covering 19 months before and 29 months after the implementation of Order 8213-B/2013, a detailing restriction policy by the competent health authority, in the quantitative phase, and 20 pharmaceutical industry interviewees in the qualitative phase.

Detailing is still the most used promotion instrument to interact with physicians, and generally the preferred one by physicians, especially more experienced ones, who tend to value the regular contact of PSRs and benefit from delivery of novelties and the prompt clarification of doubts. Detailing flow is on average the most impactful promotion instrument, with evidence coming both from the quantitative and qualitative steps of our research.

Other promotion instruments such as congresses, clinical meetings and medical literature - can also have a substantial influence in physician prescription behavior. Pharmaceutical companies pursue, through detailing, the maximization of their SOV, and the exploration of both the face to face relation and affection between PSRs and physicians, and the power of reciprocity.

The effect of detailing appears however to be smaller versus the effect observed in previous studies mainly conducted in the USA. Nevertheless, it appears that it will continue to be used as the main promotion instrument. Detailing is especially impactful in the case of younger drugs, which is consistent with the fact that most companies invest more heavily in detailing activities during the first stages of the drugs lifecycle. Also, detailing reduces the price elasticity of drugs, especially in the case of younger drugs. By other words, detailing appears to immunize, to a certain extent, doctors' awareness and perception of drug price at the moment they prescribe a drug.

Detailing is not only important in the case of current investments: past investments made in detailing activities generally have a positive impact on drug sales (carry-over effects of detailing), again especially in the case of younger or much younger drugs, while physicians are more prone to receive information about novelties. Detailing initiatives performed by competitor brands, or competitive detailing, generally have a negative impact on the own promoted drug.

The usage of iPads / Tablets grew during the period of our analysis (2012-2015) and appears to bring positive effects to the sales of the promoted drugs, probably given the novelty effect of this new communication technology, with interactive screens. However, there are some signs that this visit aid may start to saturate physicians, by limiting the spontaneity typically present in a face-to-face interaction. Printed materials including scientific articles also appear to positively impact promoted drug sales. Physicians revealing more positive future prescription intentions regarding the promoted drugs are more likely to promote them.

Another interesting conclusion is the suggestion that a high number of promoted drugs during a sales call may negatively impact the main drug promoted. We believe this may happen due to the effect of the dilution of the key messages when a higher number of products is promoted, where physicians have a limited ability to retain messages regarding several products, passed during a small period of time (the duration of a visit from a PSR). PSRs competences have been evolving, with a higher scientific approach and a communication focused on the pathology and on the benefit to the patient.

Other promotion instruments did not reveal a positive and significant effect on prescription behavior measured through elasticities, including journal advertising and direct marketing (mailing), showing almost null elasticities in our data. Many interviewees noted the perception of a negative growth of the investments in these instruments, in the interactions between companies and prescribers.

Globally, the most impactful variable on drug sales was the marketing mix variable drug price (average elasticity of -2.67). We speculate whether this strong effect may have been magnified by the deep crisis the Portuguese economy was facing during the period of our times series (2012-2015). Policy changes also strongly impact drug sales, as seen in the case of Market 1 (Blood) after the reimbursement of drugs (strong positive effect), and in Market 3 (Heart) after the loss of exclusivity (strong negative effect).

Based on the reading and analysis of Order 8213-B/2013 and on the interpretation of contributions from the interviewees, the 2013 detailing ceiling main goals were likely the reduction of disturbance on health care organizations, the reduction of prescription and consumption, the reduction of the commercial pressure of pharmaceutical companies on physicians, the safeguard of HCPs care-related activity allowing more time for assistential tasks, and the discipline and dignity of PSRs' access to HCPs and HCOs.

Most likely, Order 8213-B/2013 was not entirely implemented on a national basis, given the difficulty to control PSRs access to the NHS in a conjuncture of reduced administrative and security staff, and with no apparent audits from the tutelage. The visits' scheduling process does not likely observe the same procedures from NHS institution to institution, and in some cases the detailing ceiling was not implemented at all (at the date of the interviews). PSRs are able to make visits inside NHS institutions where they are not booked, and if exposed at most will receive a reprehension only.

The 2013 detailing ceiling had a higher effect during the first year, then losing effectiveness due to some decompression of the control, apparently absent to many of the interviewees. The North, Center, and high population regions apparently had a higher control than the South (Alentejo and Algarve) regions. Control is likely higher in certain political scenarios (in ACES). Pharmaceutical companies reacted to the ceiling mainly by increasing the investment in group sessions, in digital channels and promotion tools.

Companies appeared to use several tactics to mitigate the effect of the 2013 detailing ceiling, including visiting physicians at their private practices, using mirror visits (or Lines), waiting for the doctors in the parking or HCO entrance, or at the bar or restaurant, the registry of some of the PSRs' interactions with physicians as contacts and not as visits, and using back doors in HCOs. There was already a detailing ceiling in place, in some NHS institutions, but it was not highly controlled, it was not centralized, and it did not include a maximum number of visits per year, per NHS institution.

Order 8213-B/2013 apparently did not provoke a major impact on PSRs job or daily activity. Very likely, companies and their PSRs were able to keep the same number of visits and / or contacts as before the 2013 Order. Companies more dependent on detailing and companies with higher compliance were more exposed to the detailing ceiling, which was evident in our qualitative results, but not in our quantitative ones.

The Order apparently helped some NHS institutions – the ones that implemented and control it - to regulate and discipline PSRs access and activity inside their infrastructure, and physicians working at those institutions were likely benefited in terms of concentration and productivity, with more time for assistential tasks. But physicians can suffer from the detailing ceiling by not receiving novelties and support as often as they did before 2013.

As seen in our quantitative phase with our time series, **Order 8213-B/2013 apparently did not provoke a structural change in physician prescription behavior measured through**

detailing flow elasticities, given that not one single product evidence significant changes in its elasticities, before and after the entry into force of this ceiling, which represents the main conclusion of our thesis. At most, as addressed during the qualitative phase, it may have marginally impacted the beginning of the prescription of new medicines, less promoted in some NHS institutions**.** Much stronger than the detailing ceiling by itself are likely other measures including INN prescription, highly constraining prescription systems, expense ceilings, the economic crisis, Troika intervention, among other, who in fact created the ground for a new paradigm in the pharmaceutical industry, in Portugal.

Globally, it appears that the goals of the tutelage for the 2013 detailing ceiling were partially reached, only. Apparently there is room to improve the 2013 detailing ceiling, not only by readdressing the threshold of visits, but also by setting a different number of visits per year according to the type of company, size, type of products, and number of products promoted.

It was quite interesting to verify that, on one side of the scalar dish, the tutelage needs pharmaceutical companies' regular assistance to complement the sparse training it apparently provides to NHS physicians; on the other side of the dish, the tutelage needs to guarantee an organized and limited access of PSRs to its physicians and institutions, to assure operational efficiency and assistencial time to its patients; and physicians (especially the most senior) appreciate a regular contact with PSRs. Based on the total amount of information we were able to gather, analyze, and interpret during our research, there is the notion that this triangle of interest and collaboration will not likely be weakened in the coming years.

Table 15.1 below summarizes the accomplishment of the general and specific research goals.

Table 15.1 – Accomplishment of general and specific research goals

		Accomplished?	Comments
General objective	Determine the impact of a detailing ceiling on physician prescription behavior, measured through detailing flow elasticities	Yes	No quantitative evidence was found to confirm the existence of changes in detailing flow elasticities before and after the entry into force of the 2013 detailing ceiling
Specific objectives	Assess the relation between detailing flow and drug prescriptions	Yes	Higher intensity of detailing appears to be associated with a higher number of prescriptions of the promoted drugs. Detailing elasticity however smaller than previous research
	Assess the patterns of this relation among different therapeutic classes (markets) and products typologies	Yes	Products from different markets evidence difference detailing elasticities; detailing elasticities higher in new vs mature products; competitive detailing negatively affects own promoted drugs sales
	Assess the extent to which previous quantitative models are adequate to a Portuguese pharmaceutical industry dataset	Yes	Some models more adequate than others. New, adapted models were developed demonstrating a higher fit to the data used in the quantitative phase
	Evaluate whether the moderating effect of a detailing ceiling negatively affect detailing flow elasticities	Yes	No effect was observed in detailing elasticities, through the usage of a series break test (Chow test)
	Generate a broader, holistic understanding of the Portuguese pharmaceutical market and the dynamics of the implementation of a detailing ceiling	Yes	Multiple forces shaped the pharmaceutical industry in Portugal in the last 20 years, strongly impacting stakeholders, especially physicians, pharmaceutical companies and PSRs

Source: own elaboration

16. Limitations (global)

A first limitation of our work is the fact that we did not perform a full, systematic literature review to identify the total number of papers covering pharmaceutical marketing and regulation policy. This decision was made considering two main aspects: first, there are already literature reviews performed by Wazana (2000), Kremer et al (2008), and Spurling et al (2010), which are references in the academic community; second, we believe the methodology we observed (described earlier in our thesis) was adequate and robust, having identified the main articles in these research communities. Another limitation related to the first one is the fact that we mainly searched for literature in English, with a limited number of articles in French. We decided this after several attempts to find relevant literature in other languages, with very limited success.

As described previously in our quantitative research limitations, we had to develop a procedure to be able to calculate the detailing stock in the first 12 months of observations (from January 2012 to December 2012) using two methods, therefore this variable does not fully represent the real detailing stock for those initial months. However, as explained we believe the approach was robust and adequately performed, allowing us to use this important variable in multiple quantitative models with our data.

When analyzing the contribution to the theory, we based our critical analysis on Model 7 which, despite its global adherence to previous research conducted by many scholars investigating pharmaceutical marketing and detailing (especially in terms of the expected signals of the coefficients), has mostly non-significant coefficients, which limit the inference of our results. Nevertheless, the percentage of coefficients that simultaneously have the expected signal and are significant is in line of Leeflang & Wieringa (2010). Another limitation is the fact that our option was to directly apply several models developed by other researchers in the past, and test the extent to which they would be adequate to our data. This decision – despite resulting in many non-significant independent variables coefficients -, had to be made in order to compare our results against the outputs of the several models, allowing us to critically discuss the results in light of theory. We tried to overcome this limitation by applying Model 7 and step by step manually remove the non-significant variables. We also did not test the robustness of models 1 to 8.3 in terms of collinearity, normality of residuals, homocedasticity, and reset test, only performing it in Model 8.4, our final model.

Another limitation resides in the fact that we used, for promotion expenditures, data coming from a panel comprising a sample of physicians, whereas sales data almost perfectly

represents the population. However, IQVIA guarantees sample representativeness in terms of specialties, regions and doctor characteristics, and therefore we assumed panel full representativeness for inference purposes. Such data from IQVIA was also used, as noted before, by a great number of researchers studying time series of drug sales and pharmaceutical promotion expenditures. By other words, the inferencial part is conditional to the assumption of the correct representativeness of IQVIA doctor panel.

The model we used to run the Chow (1960) test suffered from severe misspecification (60% of products with p-values lower than 1%, and 73.3% with p-values lower than 5%). This is the equivalent to say that our model lacks non-linear variables or interactions we were not able to capture, in line with conclusions reached by Wieringa & Leeflang (2013) in their application of pharmaceutical marketing models. Despite these problems, Model 8.4 was sufficiently robust to allow us to perform the analyses, with a substantial percentage of product coefficients with signal as expected and statistically signiticant at 0,05.

One of the limitations of our qualitative phase is the fact that there were not young physicians in the list of interviewees, not allowing us to triangulate their opinions with the ones from senior physicians, in relation to different attitudes of younger versus older doctors about pharmaceutical marketing in general and especially about detailing. This option was taken in order to guarantee a specific profile of physician, with both public and private practice, and a substantial experience allowing physicians to comment on the evolution of detailing and pharmaceutical marketing, at least since the year 2005.

Another limitation is the fact that we were not able to interviewee very relevant stakeholders such as INFARMED and a high officer from the 19th Constitutional Government, that is, the one that launched Order 8213-B/2013. The contribution from INFARMED would have allowed us to understand, from the point of view of the controlling institution, how the processes of PSRs enrolment and registry work. We made several endeavors to obtain INFARMED's contribution but ended up receiving a negative response. In order to minimize the lack of a high officer from the 19th Government, and after waiting for an answer (which did not happen), we analyzed the preabule of Order 8213-B/2013, thus mitigating the absence of this critical source.

A higher number of interviewees, especially from more regions of Portugal (including the Islands), mainly physicians, PSRs and high officers from the NHS infrastructure, would have allowed a higher representativeness. Nonetheless, in order to observe very demanding timings

regarding the development of this thesis, and convinced we have a very reasonable representation of the main stakeholders, we limited the number of interviewees to 20.

17. Further Research

We believe our research provides a critical and relevant contribution to specific aspects of pharmaceutical marketing and health policy. Nevertheless, we are aware of future avenues of research, and now provide suggestions for forthcoming work. Future quantitative investigations could address the effect of a detailing ceiling on competitive detailing, to see the extent to which pharmaceutical companies adapted their detailing strategy (targeted physicians, detailing frequency, detailing volume) and may chose alternative promotion instruments to complement detailing efforts, thus following research performed by Liu et al (2016). Related to the previous topic, we also highlight the utility of studying the detailing ceiling impact on share-of-voice and on market share, to compare against results from research conducted by Liu et al (2016).

Additional quantitative research in the scope of detailing ceilings in other countries or regions is also needed to help verify the results of Liu et al (2016) counterfactual simulations which predicted that the impact on market share will be higher on drugs with a previous higher detailing intensity, whereas less detailed drugs will expand their market share.

Future quantitative research could also continue to explore the effect of a detailing ceiling on prescription behavior studying other therapeutic classes or markets in real settings. Further usage of datasets from Western European countries would be extremely valuable, given that research on this topic is still sparse in this geographic area (in line with Kremer et al, 2008), with the goal of allowing a higher generalization.

Further research is also welcome to understand different physician behavioral and attitudinal patterns in relation to pharmaceutical promotion instruments – especially detailing – according to their age interval or seniority in their clinical practice, given that the conclusions obtained in our research on this topic do not allow a total generalization considering the specific limitations highlighted on interviewed doctors' profile.

The insights gathered in relation to the real effect of Order 8213-B/2013 demands additional initiatives to study its full implementation and control, especially in the sequence of an eventual future adaptation of the Order. Further work can also study more deeply the effect of the several exogenous variables (including the GDP growth, unemployment rate, and other) in the evolution of medicines sales, from a quantitative point of view.

Finally, an interesting topic for future work is the analysis of the content and duration of PSRs sales calls and content, before and after the entry into force of a detailing ceiling, which

would contribute to research in the field of call duration (following contributions from Bernewitz (2001), Steinman, Harper, Chren, Landefeld & Bero (2007), and John (2008)), and in the field of detailing ceilings (following contributions from Larkin, Ang, Avorn & Kesselheim (2014); Liu et al (2016), and Larkin et al (2017)).

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Appendices

The appendixes are delivered in an autonomous file.

Appendix 1 – Complements to the literature review

Appendix 2 - Background of economics of health in Portugal

Appendix 3 - The pharmaceutical market in Portugal

Appendix 4 - Portuguese pharmaceutical legislative framework overview – 2000 to 2017

Appendix 5 – NVIVO additional outputs

Appendix 6 – SPSS and Eviews outputs