Studies on pharmaceutical markets

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RIJKSUNIVERSITEIT GRONINGEN

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LIST OF ABBREVIATIONS

ADE	Adverse drug event
ATC	Anatomical Therapeutic Chemical
DHPC	Direct Healthcare Professional Communication
DTCA	Direct-to-consumer advertising
EMA	European Medicines Agency
EU	European Union
GDP	Gross domestic product
GP	General practitioner
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-counter
R&D	Research and Development
Rx	Medical prescription
SmPC	Summary of Product Characteristics
WHO	World Health Organization

Chapter 1

General introduction

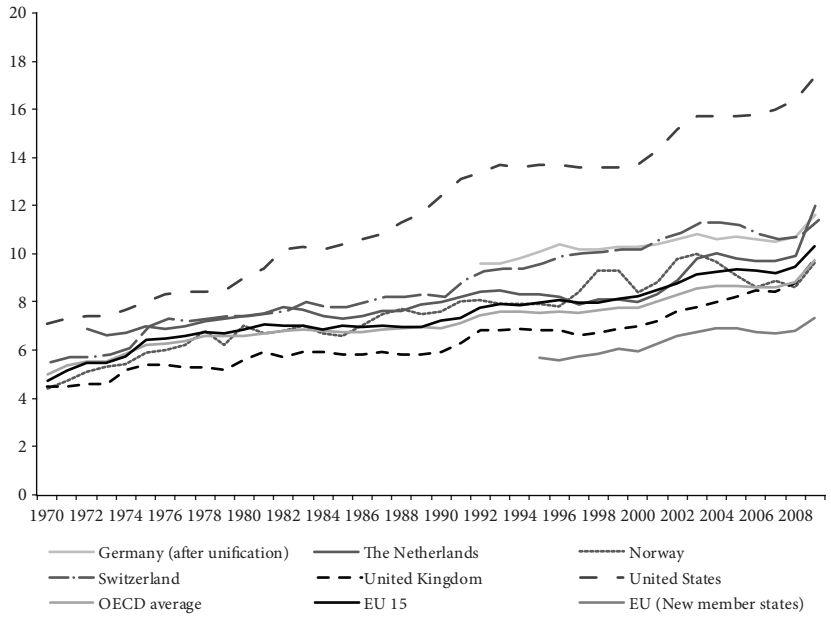
1.1 THE HEALTHCARE MARKET

1.1.1 The importance of the healthcare industry

The healthcare industry is a pivotal component of many economies worldwide. In 2010, global pharmaceutical product sales amounted to US $856 billion, including prescription (Rx) and over-the-counter (OTC)[1] medicines. It is also one of the fastest growing industries: Both public and private healthcare expenditures have experienced a steady increase and nowadays comprise a considerable portion of the GDP in many countries. EU countries spend on average 9% of their GDP on healthcare, with an average per capita spending of about US $3,000. In the US, healthcare expenditures constitute 17.6% of the GDP (compared to 5.1% in 1960) and per capita spending amounts to more than US $8,300 (see Figure 1.1). Pharmaceutical expenditures represent the third largest component of healthcare expenditures (after hospital and ambulatory care spending) and consume almost a fifth of total health expenditures across OECD countries (IMS Health 2011; OECD 2011).

[1] Over-the-counter (OTC) products can be sold directly to the consumer and do not need a prescription from a physician.

Figure 1.1: Total expenditures on health, in % of GDP



Source: OECD Health Data 2011

1.1.2 Key characteristics of the pharmaceutical market

The pharmaceutical market is a complex system in which various market participants interact with each other and which is continually evolving and changing: new drugs enter the market, public health issues are reassessed, regulatory guidelines change, and health care budgets increase and decrease. Similar to other markets, the pharmaceutical market consists of a supply-side that includes the therapy producers (e.g., manufacturers of pharmaceutical products) and a demand-side that includes patients and providers such as physicians and pharmacists (see for an overview of the players, Manchanda et al. 2005). However, the pharmaceutical market operates differently than a regular consumer goods market. The idiosyncrasies derive from the fact that the physician, rather than the end consumer, is the main decision maker; that health care costs are largely covered by third-party payers, which results in low price elasticity of demand; and that exclusive patent rights and regulatory constraints for pharmaceutical products exist. The latter is a consequence of the inherent characteristics of pharmaceutical

products[2]. They differ from regular consumer goods in two important aspects: First, inherent uncertainty exists about risks and side-effects when prescribing or taking the drug, and wrong decisions can involve serious health consequences. Second, the quality of a drug can seldom be judged immediately but only after sufficient information has been gathered through carefully controlled studies of large patient samples. This is because the effects of a drug largely depend on the individual patient's treatment history, co-morbidity, and characteristics such as age or gender.

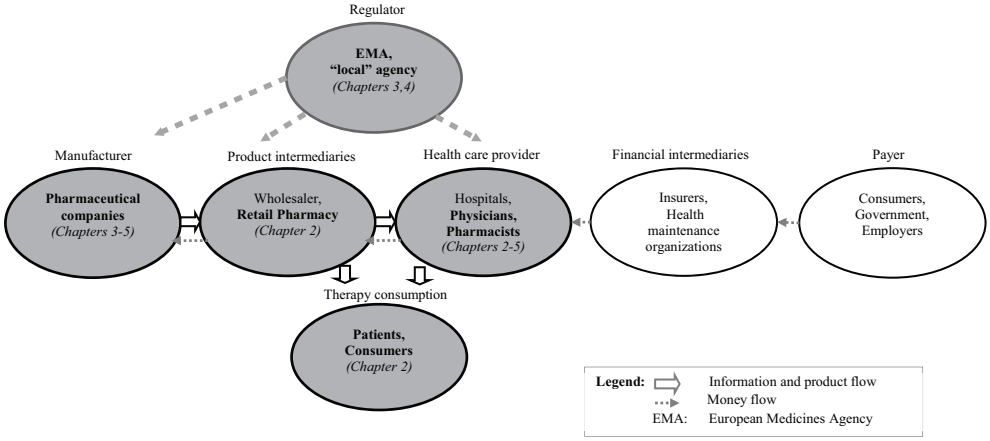
Usually, the consumption decision involves the participation of several parties: There is not only the prescribing physician who takes a key responsibility in therapy choices; other parties such as third-party payers influence the decision over which drug(s) should be used to treat a patient's health condition. Health insurers decide upon reimbursement and incentive schemes, and governments restrict access to and choice of medications through regulation. Rarely do patients bear the full cost of the drug, but depending on the particular regulatory and reimbursement regimes they may be asked to pay some portion of the treatment prescribed. Due to their professional knowledge, pharmacists also play a vital role in dispensing and selecting medical products, both prescribed and over-the-counter products. Moreover, the pharmaceutical industry itself has significant impact on the market by developing new products and coordinating the levels of drug utilization through marketing communication. Of course, patients today more actively engage in treatment decisions, shifting the traditional (paternalistic) doctor-patient relation towards a more participatory relationship (Camacho et al. 2010; Guadagnoli and Ward 1998). All of this is embedded in a regulatory environment that needs to balance health policy objectives against industrial policy objectives in a changing healthcare environment. Figure 1.2 illustrates the different players in the market.

The healthcare industry poses marked challenges to academics, industry practitioners, and policy makers (Stremersch and van Dyck 2009). For example, governments are currently confronted with rising health care costs due to demographic changes and the high costs of new medical treatments. Simultaneously, there is growing pressure on companies to develop new, innovative drugs (Kaitin 2010). This drug development process is extremely uncertain, characterized by the high costs and attrition rates of new compounds. Of 5,000-10,000 new inventions, only 10 to 20 enter the clinical studies and eventually only one reaches the market place (IFPMA 2011; Kola and Landis 2004). New therapies need to demonstrate that they are efficacious and safe before they can be approved for marketing. Drug manufacturers that develop new pharmaceuticals get exclusive marketing rights for a limited period of time,

[2] A pharmaceutical product is defined as a substance or combination of substances administered to human beings in order to prevent, diagnose, alleviate or cure a disease, to relieve a symptom, or to modify bodily function in some way. In everyday language the terms medicine or drug are more common. In this thesis the three terms are used interchangeably.

which permits them to recover their R&D investments.[3] Generally, pharmaceutical products enjoy a minimum patent term of 15-20 years, depending on country law, from the filing date on; however, the effective patent length is much shorter as companies apply for a patent early in the development process (EFPIA 2008).

Figure 1.2: Important players in the healthcare market



Adapted from Burns (2005), Stremersch and van Dyck (2009)

Once the patent expires, generic products – the unbranded equivalents of the branded drugs – can enter the market and brand-name drug sales rapidly decline. What causes this is the originator's reduction in marketing expenditures when patent expiration approaches (Gonzales et al. 2008; Osinga 2011). To what extent generic drugs are substituted for their branded counterparts largely depends on the specific reimbursement schemes and financial incentives given to patients and care providers.

Because of the importance of this industry and its societal influence, healthcare marketing has recently become a more prominent item on the research agenda of marketing scholars (Manchanda et al. 2005; Shankar 2008; Stremersch and van Dyck 2009). Three main research themes have been identified, each possessing its own challenging problems: therapy creation, e.g., pipeline optimization and innovation alliance formation; therapy

[3] Pharmaceutical companies worldwide have spent over US $120 billion on R&D in 2009 - that is 19% of total prescription sales (IFPMA 2011).

launch, e.g., new drug adoption and key opinion leader selection; and therapy promotion, e.g., communication management and targeting, as well as compliance (Stremersch and van Dyck 2009).

1.2 OUTLINE OF THE THESIS

In this thesis we aim to provide insights into three crucial aspects that touch upon the key research themes, namely how to

- Ensure retail pharmacies' sales performance in a changing health care environment.
- Ensure that new safety information about marketed drugs is communicated effectively such that the continued appropriate use of these drugs can be assured.
- Ensure rapid market adoption of new drugs and allocate scarce promotional resources efficiently.

The thesis is divided into three parts, with each one covering a particular aspect of the pharmaceutical marketplace (Figure 1.2). Each part is further subdivided into chapters which will report on a separate study. Table 1.1 presents this outline.

Table 1.1: Outline of this thesis

	Chapter	Research setting	Aims	Key findings	Managerial insights
Part I	Chapter 2	*Market*: OTC products *Main players*: Pharmacies, Consumers	Investigation of the impact of sales performance drivers on OTC drug sales in retail pharmacies.	Assortment and promotions enhance pharmacy sales performance. Traditional retail store and location factors appear to be less important in a retail pharmacy setting.	Better understanding of the factors that can enhance retail pharmacy sales performance. Importance of combining marketing and healthcare expertise to stay competitive in a changing healthcare environment.
Part II	Chapters 3&4	*Market*: Prescription medicines *Main players*: Regulator; Pharmaceutical companies; Physicians	Assessment of the effect of drug-safety warnings (i.e., DHPCs) on new prescriptions.	Safety-related regulatory actions lead to decreased usage in the short-term in ~ 50% of the cases. Only a minority of drugs with a DHPC show substantial long-term reductions in use.	Better understanding of the effectiveness of communicating drug-safety warnings. Provide guidance to public health officials and pharmaceutical manufacturers on how to improve the impact of safety warnings by tailoring DHPCs and risk communication interventions more specifically.
			Exploring the impact of drug and DHPC related characteristics on the effect of DHPCs on drug use.	Specialist drug, DHPC template availability, seriousness of the safety issue, and pre-DHPC trend in use are important determinants that influence the impact of DHPCs on drug use.	
Part III	Chapter 5	*Market*: Prescription medicines *Main players*: Pharmaceutical companies; Physicians	Examining the impact of marketing communication, different stages of the adoption process, and physician characteristics on new drug prescribing. Demonstrating the importance of physician level information and adoption stage when allocating detailing activities.	There is considerable variation in physicians' propensity to prescribe and their sensitivity to detailing. Loyalty, prescribing volume, and share of wallet are the most important drivers that explain this variation. The relevance of these drivers changes during the adoption process.	Better understanding of the relevance of individual physician characteristics and their stage in the adoption process. Assist managers in formulating better detailing targeting strategies and thus allocating promotional resources more effectively.

In the following discussion we provide a short preview and some background information on the remaining chapters.

1.2.1 Retail pharmacies and the over-the-counter market

Retail pharmacies are an integral part of the pharmaceutical market. In their function as healthcare provider, they deliver independent pharmaceutical care as well as advice to patients/consumers on the appropriate use of medicines. This function competes with commercial elements that arise from their role as retail businesses (Schmidt and Pioch 2004; van Mil and Schulz 2006).

For a long time, retail pharmacies' traditional core 'product' and primary income source has been the supplying and dispensing of prescription medicines. Market deregulation and new health care policies, along with rising societal expectations, have helped alter the role of retail pharmacies. Meanwhile, their role has expanded from the mere supply of pharmaceuticals to the delivery of extended health care services in order to meet both the changing demand of consumers and the retail environment (Taylor et al. 2004; van Mil and Schulz 2006). Retail pharmacies today are taking an active part in the management of medication therapy and in the support of other health professionals (Nissen 2011). This transition coincides with a growing interest in self-medication. This trend is further promoted by governments that see self-care and the use of non-prescription products as a way to curtail healthcare costs.

At the same time, the market for OTC products is rising. In 2010, the global OTC drug market was worth about US $73 billion, and growth rates exceed those in the prescription drug market (IMS Health 2010). This has been encouraged by recent drug deregulation measures that facilitate the reclassification of prescription-only to over-the-counter status. Consumers, confronted with a wider range of OTC drugs, may increasingly turn to pharmacies for help in choosing the right medical treatment, which, in turn, puts more responsibility on retail pharmacies to inform and educate consumers on the safe use of self-medication products (Wertheimer and Serradell 2008). The greater availability, coupled with the weakening of regulatory constraints on the retail supply of OTC drugs, has intensified the competitive pressure, especially as drugstores and mail-order dispensaries expand their share in the OTC business.

The ongoing deregulation of pharmaceutical distribution has great impact on the retail pharmacy sector. Notably, retail pharmacies are challenged by structural changes resulting from an increase in both vertical and horizontal integration. Pharmacy remuneration schemes are threatened by regulatory mechanisms that seek to encourage high-quality, but more cost-

effective care provisions (Macarthur 2007; Vogler et al. 2012). In view of these developments, OTC products are becoming an important business segment for retail pharmacies. They can create new opportunities for extended healthcare service; yet a stronger commitment to the commercial aspects of their business will be necessary to remain competitive (Schmidt and Pioch 2004).

Despite their relevance in the healthcare value chain and their increasing responsibility in drug therapy decision-making and advice-giving, retail pharmacies have been largely neglected by health marketing scholars (Stremersch 2008). We address this gap in the first part of the thesis (Chapter 2) where we investigate the effect of different market(ing)-related characteristics on retail pharmacies' performance in the OTC category. In doing so, we aim to increase our understanding of the factors that can help improve pharmacy revenues. This question is particularly interesting given the ongoing liberalization in the healthcare sector across Europe and the challenges involved for retail pharmacies.

1.2.2 Pharmaceutical regulation and risk communication

Part II consists of Chapters 3 and 4. The central theme of both chapters is the effectiveness of regulatory activity, and specifically the communication about drug safety issues undertaken to ensure an effective and safe drug usage. The success of these communication measures rests to a great extent on whether and how they are translated into daily practice. Yet, available evidence from past research has raised questions about their effectiveness (Goldman 2004; Yu et al. 2011).

The pharmaceutical industry is known as one of the most regulated industries in the world. Regulation comes in the form of tight safety norms, stringent approval processes, and control regimes affecting many facets of the drug's development, its manufacturing, distribution, pricing and marketing (Mossialos and Oliver 2005; Stremersch and Lemmens 2009).[4] The fundamental purpose of regulation is to ensure that products are safe and effective in order to protect public health. This has appeared to be not always a simple task: being indispensable for health and quality of life for many people, drugs inherently bear potential risks of undesirable side effects that have caused harm and severe adverse incidents in the past; prominent examples include the withdrawals of Vioxx or Avandia, the latter being the biggest-selling diabetes drug.

Jerry Avorn, a Harvard Medical School researcher, once compared medicines with automotive vehicles: the world of drugs has many biochemical Volvos – reliable, useful, and

[4] See also the European Commission's Regulation (EC) No 726/2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf.

safe enough to reduce the risk of harm to its user, even in an accident. Rarely, a pharmaceutical product will appear that is more like a Pinto: inherently dangerous, likely to crash and burn even with normal use. Most drugs, however, are more like midsize Chevrolets. They work reasonably well, and their safety has much to do with how they are used. The same Chevrolet can be all utility and no risk when driven by the legendary little old lady schoolteacher, but turn into a hazardous killing machine in the hands of her drunken teenage grandson (from: *Powerful Medicines 2005*).

Typically, a drug's complete benefit-risk profile is not immediately obvious but can only be assessed when the drug has been used for a long time and in real-life settings (Garrison 2010). Therefore, a lifecycle approach to drug evaluation has become a central element of early detection and risk minimization strategies (Mol et al. 2010). Ongoing initiatives intend to promote more proactive risk management programs and provide timely and accurate information to healthcare professionals (and patients) about the safe use of drugs (Raine et al. 2011). One example of such activity involves letters to healthcare professionals, known as 'Dear Healthcare Professional Communications' (DHPCs) or 'Dear Doctor Letters'.

A shortcoming of most previous research on the effectiveness of safety-related regulatory actions is their focus on either case studies or small-scale studies. The aim of our studies in Chapter 3 and Chapter 4 is to (1) assess the impact of a considerably larger amount of DHPCs and safety issues on drug use, thereby expanding the currently limited knowledge about their effectiveness, and (2) explore potential factors that could influence the effectiveness of risk communication. More specifically, in Chapter 3 we examine the short- and long-term impact of drug safety warnings (i.e., DHPCs) on drug use in the Netherlands. Based on data from 58 drug and DHPC pairs over a period of nine years, we assess changes in new drug prescriptions using an interrupted time-series design, where the intervention is the DHPC. In Chapter 4 we propose several drug and DHPC characteristics which may influence the effectiveness of drug-safety warnings.

1.2.3 New drug adoption

For pharmaceutical firms it is crucial that the benefits of their innovative drugs are effectively communicated and that the product is quickly adopted so to ensure recovery of their high R&D efforts (Sorescu et al. 2003). Rapid adoption and diffusion of innovative drugs is also important from the patient's point of view if said drugs demonstrate superior effectiveness or fill unmet medical needs. The resulting improved health outcomes will eventually serve public policy interests.

Previous studies have identified several underlying drivers of new drug adoption (e.g., Fischer et al. 2010; Manchanda et al. 2008; Narayanan and Manchanda 2009; Ruiz-Conde et al. 2009). For example, product characteristics such as order of entry and quality are proven crucial factors of new product success (Fischer et al. 2010). Country-specific factors such as regulatory regimes or developed versus developing nations are shown to also influence the diffusion of new pharmaceuticals (Desiraju et al. 2004; Stremersch and Lemmens 2009; Verniers et al. 2011), and pharmaceutical marketing is suggested to not only accelerate diffusion but also help obtain higher diffusion rates. Pharmaceutical marketing efforts can be directed to the prescribing physician (in the form of visits from sales representatives also known as detailing, meetings and symposia, free drug samples, as well as medical journal advertising) or directly aim at the consumer (referred to as direct-to-consumer advertising, DTCA). Across Europe, DTCA of prescription drugs is banned by health authorities, making this type of marketing instrument less relevant to our context. In those countries where DTCA is allowed it has rapidly risen as a share of total promotion (see e.g., Liu and Gupta 2012b, for a review on DTCA).

The predominant direct-to-physician marketing activity is detailing (Manchanda and Honka 2005). For the most part, academic literature in marketing has shown that detailing has a significant effect on physician prescription behavior (e.g., Fischer and Albers 2010; Gönül et al. 2001; Kremer et al. 2008; Leeflang and Wieringa 2010; Manchanda and Honka 2005). Furthermore, the effectiveness of pharmaceutical marketing depends on the prescriber, the product that is detailed, the market, and product life cycle (Chintagunta and Desiraju 2005; Manchanda and Chintagunta 2004; Narayanan et al. 2005; Osinga et al. 2010; Venkataraman and Stremersch 2007).

Another central theme in new product adoption research has been (and still is) the modeling of individual adoption decisions. It is well accepted that considerable heterogeneity exists across physicians in whether and when they will adopt a new drug and how they respond to different marketing stimuli. Also, marketing efforts can have differential impact on physicians' adoption decision depending on their stage in the adoption process (Montoya et al. 2010; Narayanan et al. 2005; Rogers 2003). Despite an increased interest in improving our understanding of new drug adoption, and in particular why and how new products are accepted differently, little research has been conducted that combines the different sources of heterogeneity within one framework. Knowing which physicians are most receptive to marketing actions and when they are most receptive is also managerially relevant, for it helps managers make better targeting decisions. We address these important issues in Part III (Chapter 5) where we study the interplay between marketing efforts, stage in the adoption

process, and physician characteristics on the prescription of a new drug. We propose a method that also considers which physicians should be approached with detailing efforts in the different stages of the adoption process and demonstrate that taking into account both physician-level information and the adoption process will lead to more effective targeting.

In sum, the aim of this thesis is to study important aspects of the healthcare industry that cover the prescription drug and the over-the-counter markets, that involve manufacturers and physicians as healthcare providers, and retail pharmacies as product intermediaries, and whose scope of activities is defined within the boundaries of an overarching regulatory policy framework. In this thesis we provide valuable insights that both advance our knowledge and help policy makers and other stakeholders to formulate better strategies that increase the effectiveness of policy and marketing decisions. In Chapter 6, we take on the challenges for firms and policy makers, and provide directions for future research.

Part I

Chapter 2

Improving pharmacy store performance: the merits of over-the-counter drugs

2.1 INTRODUCTION

Across the world, comprehensive liberalization and deregulation reforms are affecting economic sectors that formerly enjoyed a monopoly position or featured solely state-owned enterprises, as exemplified by the transportation, telecommunication, gas, and energy sectors (Geradin 2000; Wieringa and Verhoef 2007). These reforms introduce increased competition and attract new suppliers that compete with incumbents by offering improved price or service quality.

In addition, many European countries have started to implement pro-competitive policy measures in the healthcare market, including its retail pharmacy sector (Anell 2005; Vogler et al. 2006). In the United States, heavy deregulation of the pharmacy sector happened much earlier and with a much broader scope.[5] But the European pharmacy market has long been tightly regulated, with restrictions that apply to ownership, market entry and location, and the scope of activity. For example, in many countries only pharmacists could own pharmacies, and the number of outlets was based on the population size. Pharmacists' core purpose was to dispense and provide medicines and pharmaceutical care (Schmidt and Pioch 2004; van Mil and Schulz 2006). In turn, their pharmacies generally lacked even basic business

[5] The U.S. market is dominated by large retail pharmacy chains, similar to retail drugstore chains, such as Walgreens, together with 'pharmacy corners' located in major supermarkets or discount stores, such as Walmart.

competences. The liberalization of the retail pharmacy market and over-the-counter (OTC)[6] drug deregulation in Europe has relaxed some of these restrictions (though the extent of deregulatory measures differs, according to each nation's legislation), which has considerably altered the competitive environment, fostered the emergence of new entrants and nationwide pharmacy chains, and expanded OTC product dispensing beyond pharmacy outlets (Anell 2005; Vogler et al. 2006).

Healthcare cost containment and the wish to lower public expenditures have been the main motives for liberalizing the market, though extensive supply-side regulation also is required to provide equal access to and quality of care (Volkerink et al. 2007). By introducing more favorable competition policies, the scope of government interventions irrevocably diminishes, but this free play of market forces can have negative effects on consumer welfare and public health. Still, liberalization reforms continue to alter the retail pharmacy landscape, in terms of both ownership (e.g., multiple pharmacy ownership, pharmacy chains) and the composition of the sector's participants (e.g., vertical integration between wholesalers and pharmacy outlets, entry of new suppliers; Anell 2005; Vogler et al. 2012).

Norway and Iceland represent the forefront of this process. In both countries, new policies have altered the competitive structure of the pharmacy market and led to increases in the number of pharmacy outlets and the formation of nationwide pharmacy chains through horizontal or vertical integration (Almasdòttir et al. 2000; Anell and Hjelmgren 2002). Similar changes in market structure and competition are expected or have been witnessed in other European countries that followed the Scandinavian example (Vogler et al. 2012). Parallel with market liberalization has been an increase in the number of products moved from prescription-only (Rx) to OTC status; as a result, more OTC products have become available in outlets outside pharmacies. This process has been supported by governments that seek ways to pass some part of the health cost burden to consumers (i.e., OTC products are generally excluded from third-party reimbursement). It also reflects growing awareness and preference for self-medication, which has changed consumers' health therapy consumption patterns (Ling et al. 2002).

Along with these developments comes a change in the role of traditional pharmacies. Beyond their role as healthcare providers, pharmacies must respond to an environment in which consumers demand easy access to a variety of medicines and pharmaceutical advice (Taylor et al. 2004; van Mil 2005). Because non-prescription medicines provide common

[6] Over-the-counter (OTC) products comprise medicinal and health care products that are available to consumers without a prescription, so no physician consultation is needed. The EU legislation defines a medicinal product or drug as any substance or combination of substances presented for treatment or prevention of disease in humans, or which may be administered to humans with a view to restoring, correcting or modifying physiological functions. Supplements such as vitamins and certain cosmetics fall within this definition.

therapy choices for many people, without any advice from physicians, retail pharmacies' professional components and qualified staff may provide a competitive advantage over other (non-pharmacy) retailers, such as drugstores or supermarkets. The OTC products accordingly may represent a facet for improving pharmacy performance, enabling pharmacies to differentiate themselves from their competitors (McGee et al. 2000). The importance of OTC products for retail pharmacies, as an additional source of revenue, also has increased as European governments have adopted tendering-like systems of price fixing and pharmacy remuneration that diminish the revenue potential of traditional pharmacies (Kanavos et al. 2009).

In summary, the deregulation of the previously regulated pharmaceutical market imposes challenges for traditional retail pharmacies, particularly as the market grows increasingly competitive. Therefore, retail pharmacies must shift their current business model to develop a more commercial view, including (retail) marketing competences, if they are to survive the financial and competitive pressures on them (Macarthur 2007; Schmidt and Pioch 2004).

Prior retailing literature contains multiple studies that investigate the determinants of retail store performance (e.g., Kumar and Karande 2000; Pan and Zinkhan 2006; Reinartz and Kumar 1999). Among the most frequently cited determinants are marketing mix variables, such as promotions and assortment, environmental characteristics, such as competition, and store variables, such as size or image. Yet the vast majority of studies in this field concentrate on grocery stores or supermarkets. Despite the tempting notion of proposing that retail factors that have proven successful in the consumer goods market will be important in the pharmacy market, virtually no empirical evidence exists to justify this application to the retail pharmacy context.

In some respects, OTC products do not differ much from regular consumer goods: The end consumer – not, as in the prescription drug market, the physician – makes the decision to select and consume OTC products. Because OTC products can be purchased without any physician intervention, controls to support their appropriate use are required (WSMI 2007). Furthermore, marketplace competition and out-of-pocket payments for non-prescription products influence OTC product choice. Yet there also are important differences between the OTC and consumer goods markets. In particular, OTC products can be experience or credence goods:[7] The evaluation of their effectiveness is fairly difficult, because drugs have patient-specific effects (Katz 2007). They also have the potential for harm; because there

[7] Experience goods possess unknown characteristics that can be revealed only after consumption. Credence goods are those whose utility cannot be discerned even after consumption.

is no supervision from a medical doctor, regulatory rules regarding labeling (e.g., patient information leaflets) and advertising claims exist to promote consumer information and education. From a public health perspective, OTC drugs are medications rather than regular consumer goods (Wazaify et al. 2005).

As this discussion indicates, it is critical to investigate retailing strategy opportunities to improve pharmacy performance in a competitive OTC market. Considering the role pharmacies play in the healthcare value chain, such an investigation is also highly relevant (Manchanda et al. 2005; Stremersch 2008). Accordingly, this chapter summarizes an exploratory study in the Dutch pharmacy market, in which we aimed to identify crucial factors to explain differences in performance between the various pharmacy outlets of one chain. We empirically examine which product, store, customer, and competitor characteristics enhance OTC category sales and store performance. This effort should advance understanding of the marketing activities that determine sales performance in the pharmacy sector. We elucidate whether there are similarities between factors that determine the sales of OTC drugs and factors that affect sales of convenience products. By adding subjective indicators (i.e., customer perceptions) to objective market and store characteristics, we offer insights into their relative importance and effectiveness as performance drivers. We also demonstrate that the combination of scanner-based and consumer-level data enables us to link important variables in this market. Some prior studies consider the link between unobservable measures (e.g., customers' perceptions) and performance, whereas others note the direct link between firm or retail strategies (e.g., marketing actions) and performance, without addressing unobservable constructs (for a review, see Gupta and Zeithaml 2006). Our study also complements sparse literature on marketing for OTC pharmaceuticals.

We identify assortment and promotions as crucial determinants of pharmacy performance. The empirical findings further indicate that location factors that are critical for traditional retailers may be less significant for retail pharmacies. The results thus can help retail pharmacies cope with the ramifications of a deregulated healthcare market and determine how to address it using marketing strategies.

The remainder of this chapter is organized as follows: We describe the context of the study, then provide a summary of relevant literature related to two main domains of interest, namely, over-the-counter products and drivers of store performance. We then describe the data and present the modeling framework. After discussing the findings, we conclude this chapter with some study implications and limitations.

2.2 RESEARCH SETTING

The Dutch pharmacy market generally has been more liberal than other European countries'. Non-prescription medicines have been sold outside licensed pharmacies, at drugstores, for more than a century. Theoretically, no restrictions limit the establishment of new pharmacies or locations. However, the prerequisite for contracts with health insurance companies, as well as the existing relationships among established pharmacies or between general practitioners and pharmacies, tend to hamper new market entry (Mossialos and Mrazek 2003). Since the late 1980s, the restrictions on ownership have been reversed, such that multiple ownership and ownership by non-pharmacists is possible, though the latter form requires supervision by a trained pharmacist (Vogler et al. 2012). Additional reforms to stimulate competition quickly followed. The range of OTC products, as noted previously, broadened as a result of new deregulations on medicinal products. Simultaneously, the scope of pharmacy practice has expanded, from dispensing medicines to providing pharmaceutical care (Mossialos et al. 2004; van Mil and Schulz 2006).

After deregulation, the number of alternative retail pharmacy channels (e.g., mail-order, Internet) and chain-based pharmacies continued to increase. In addition, more vendors from outside the industry entered, competing for customers and a share in the OTC business (Taylor et al. 2004; Vogler et al. 2012). The pharmacy business was further affected by a series of reforms in the context of privatization of the Dutch health insurance market. Typically, Dutch retail pharmacies enjoy two main sources of revenue: a fixed dispensing fee and the difference between the market price and the reimbursement they receive from the insurer (Maarse 2009). In 2005 a 'joint preference policy' introduced for three active ingredients – simvastatin, pravastatin, and omeprazole – allowed health insurers to reimburse only for the least expensive product within a group that contained the active ingredient. In 2007, this policy was extended as an 'individual preference policy,' which operates in a similar manner except that insurance companies can also individually designate preferred pharmaceuticals. These measures have had important consequences for pharmacies' profits. Their purchasing margins on generic medicines, which once represented a major source of revenue, have dropped significantly due to their lost negotiation power. For example, retail pharmacies previously would negotiate with manufacturers and wholesalers to receive price discounts; under the preference policy scheme, this negotiation power has shifted away from pharmacies towards health insurers (Kanavos et al. 2009; Maarse 2009). The rising pressure on retail pharmacies' profitability inevitably has created growing tension between professional and commercial interests (van Mil and Schulz 2006).

2.3 MARKETING OVER-THE-COUNTER PHARMACEUTICALS

A relatively small body of research explicitly addresses OTC product decisions in a marketing context. Recent market developments have increased the complexities of OTC drug therapies and consumers' decision-making processes, making product selection more and more difficult (ISMP 2007). Unlike consumers of ethical drugs, which are prescribed by a physician, OTC drug consumers rely on their own judgment. These consumers likely perceive some risk in self-diagnosing and determining their most suitable treatment. Particularly in health service encounters, it is important to reduce consumers' perceived risks and develop positive attitudes towards repeated interaction and cooperation (Grewal et al. 2007). Although OTC products often are available in other retail sites, many patients seeking an OTC solution to their health problems still prefer to receive guidance from a pharmacist (Hong et al. 2005; Simoens et al. 2009).

Because the effect of a drug on health conditions can be learned only through use, prior experience with and knowledge about the product play significant roles in purchase decisions (Akçura et al. 2004; Gönül 1999). The quality of most (fast-moving) consumer goods can be ascertained relatively easily before or shortly after purchase, unlike the case for drugs. Instead, quality with regard to efficacy and safety is not readily observable and can be determined only after considerable time, if at all. Because of the difficulty of obtaining such information about the drug's quality, patients are reluctant to switch when they have found a drug that works for them (Gönül 1999). Furthermore, prior purchases of a brand, rather than price concerns, likely govern actual OTC drug purchases (Gönül 1999). Consumers' low price sensitivity for OTC drugs is confirmed by Akçura et al. (2004); when other quality cues are missing, price signals quality, and patients tend to choose more expensive drugs. Price promotions therefore might not enhance sales performance; other promotional tools (e.g., conspicuous displays, meaningful features) and nonprice marketing instruments may have more impact (Ling et al. 2002).

2.4 DRIVERS OF STORE PERFORMANCE

Retail performance drivers, in terms of store, customer, and competitor characteristics, and their impacts on store sales have been studied extensively (e.g., Kumar and Karande 2000; Pan and Zinkhan, 2006; Reinartz and Kumar 1999). In response to retailers' growing interest in exploiting heterogeneous consumer preferences, retailing scholars focus on micromarketing,

or tailoring marketing strategies to local conditions (e.g., Campo et al. 2000; Campo and Gijsbrechts 2004; Hoch et al. 1995; Montgomery 1997). The recent application of special econometrics and structural models has allowed research on store performance to address simultaneously outlet location and marketing mix decisions in the context of unobserved spatial demand and competition (e.g., Duan and Mela 2009; Hunneman 2011; van Dijk et al. 2004; Zhu and Singh 2009).

Store performance can be assessed in several ways, including retail patronage, store traffic, store profits, and overall sales (Reinartz and Kumar 1999). However, aggregated sales measures seem to ignore differences in sales of products in particular categories by an individual store, so assessments at a more disaggregate level (e.g., category) may provide a better basis for developing efficient strategies (Campo et al. 2000; Grewal et al. 1999). In line with previous research, we consider several sales performance drivers pertaining to the market in which the store operates, as well as to the store outlet itself.

2.4.1 Market characteristics

2.4.1.1 Competition

Competition is an important determinant of store performance (Campo et al. 2000; Cleeren et al. 2006). Typically, stores that lie within a certain distance or within the trading area are competitors (see Campo et al. 2000; Hoch et al. 1995; Montgomery 1997). Distance measures, such as the (average) distance to the nearest competitors or the number of market players, serve to assess the level of competition (e.g., Hoch et al. 1995; Montgomery 1997). Van Dijk et al. (2004) suggest using store choice data or managerial expertise to specify competition and thereby avoid falsely excluding relevant competitors because of arbitrarily defined distance measures. With respect to the effect of competition, mixed results emerge. Some studies confirm a negative effect of competition on store performance (Cleeren et al. 2006; Hoch et al. 1995), whereas others find that the presence of more competing outlets relates positively to sales performance (Campo et al. 2000). Campo et al. (2000) explain their finding of a positive effect of competition by noting that trade areas with greater economic potential not only increase their own sales but also attract more competitors.

2.4.1.2 Sociodemographic control variables

Prior research documents the influence of sociodemographic characteristics, such as income, age, and household size, on a store's performance, due to their differential impact on purchasing power, buying behavior, and store choice (e.g., Hoch et al. 1995; Kumar and Karande 2000; Reinartz and Kumar 1999). People with higher income tend to confront higher opportunity

costs for their time and often are more disposed to pay for convenience (Reinartz and Kumar 1999). In contrast, elderly people and larger households may face more severe budget constraints and therefore are more price conscious. Elderly consumers also have different needs and preferences for products and services, which influence their store choice decisions (Moschis and Friend 2008). They tend to prefer stores with known reliability and want help choosing among products. The limited mobility that elderly people often experience leads them to emphasize the ease of reaching a store and distance to it as more important reasons for patronizing a specific outlet (Moschis et al. 2004).

2.4.2 Characteristics pertaining to the store outlet

2.4.2.1 Store location

The location of a retail outlet is an important determinant of success and a potential source of market power. Consumers consider different criteria when assessing their total shopping cost, and the effort to reach the store is one of them. Consequently, the location of a retail outlet is a vital determinant of success through its influence on consumer patronage (Arnold et al. 1983; Kumar and Karande 2000). Because of its importance in previous models of store performance, we include a location indicator that measures how isolated a store is, along with a distance measure, because the centrality of a retail site and a more convenient location enhance retailer performance (Craig et al. 1984; Pan and Zinkhan 2006).

2.4.2.2 Store size

The size of a store can help explain retail store performance, as an indicator of assortment availability, convenience, or service levels (Campo et al. 2000; Campo and Gijsbrechts 2004).

2.4.2.3 Image

Chain and store image affect retail patronage and thus category and store sales (e.g., Baker et al. 2002). Image generally stems from consumers' evaluations of salient store attributes, such as its accessibility, atmosphere, in-store service (e.g., information provided), and promotions (Kasulis and Lusch 1981; Martineau 1958). Store image literature thus has distinguished different store attributes as part of the overall image of a store, and various measurement methods attempt to capture the numerous and complex attributes. Moreover, the relative importance of certain components likely varies across markets, regions, competitive situations, and customer segments (McGoldrick 2002).

2.4.2.4 Assortment

Empirical research indicates that product assortment and its composition play critical roles in influencing retail patronage and customers' purchase probabilities for a specific option (Pan and Zinkhan 2006), which in turn affect store/sales performance. Inherently related to assortment is variety. Studies note that including additional products increases consumers' preferences for an assortment (Oppewal and Koelemeijer 2005), whereas failing to provide an expected assortment can invoke serious sales losses through customer defects (Borle et al. 2005; Campo et al. 2004). Therefore, assortment variety may be among the most important reasons consumers give for patronizing a certain store (Briesch et al. 2009; Hoch et al. 1999). Furthermore, consumers tend to trade off convenience and the importance of the assortment (Briesch et al. 2009). By offering greater variety, the retailer enhances shopping convenience, because customers can make more purchases during a one-stop trip, which minimizes the specific costs involved in each shopping trip (e.g., travel time, effort). By tailoring their assortments to local needs rather than making national (chain)-level assortment decisions, retailers also can better serve heterogeneous consumer tastes (Dhar et al. 2001).

As this brief review shows, the importance of category-specific differences in both attracting customers and enhancing sales has prompted broad consensus in retailing research. Location-specific category management benefits retailers, because it helps them allocate scarce resources, which eventually translates into improved performance (e.g., Campo and Gijsbrechts 2004).

2.4.2.5 Impulse proneness

Impulse proneness can be either a category characteristic or a consumer trait. We follow Narasimhan et al. (1996) and define impulse proneness as a category characteristic. Thus, the degree of impulsiveness that marks a category refers to the extent to which people purchase from that category without forethought. Purchases in impulse categories generally occur without advance planning (Narasimhan et al. 1996), so more impulse categories can enhance a store's sales volume. Ailawadi et al. (2006) propose that customers buy more when they recognize an impulse category on promotion, though this effect may be small in drugstores, which customers usually visit to buy specific health and beauty products. A similar argument may apply to pharmacy outlets.

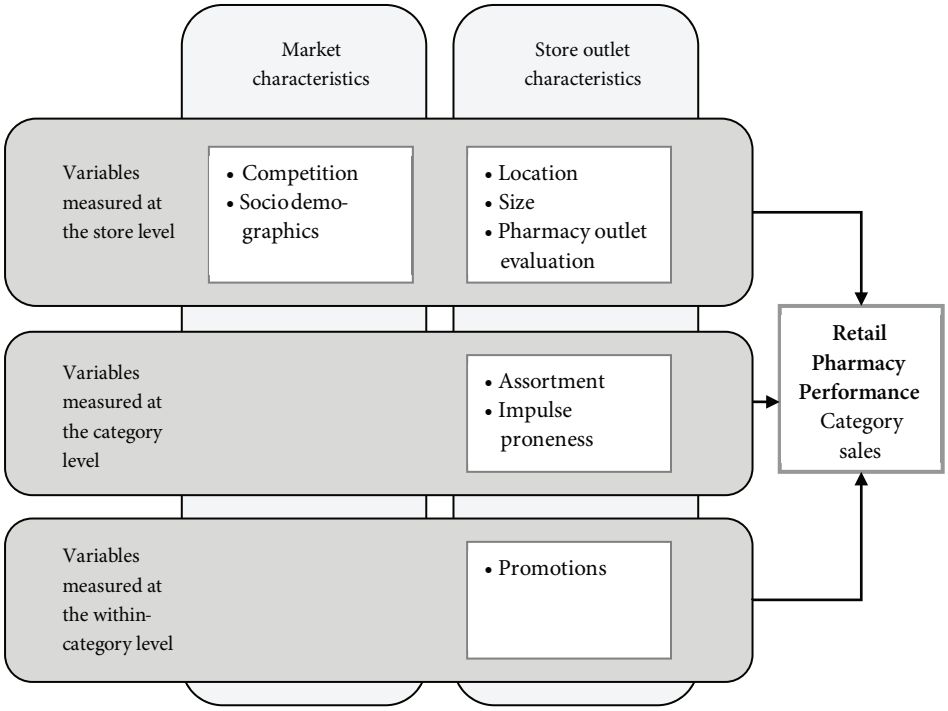
2.4.2.6 Promotions

Various studies have investigated the effects of promotions, such as features, displays, or price cuts, on sales. Empirical generalizations reveal that promotions have substantial effects on short-term sales (for reviews, see Hanssens 2009; van Heerde et al. 2002). Promotions can affect

retail sales through five important mechanisms: brand switching, store switching, category expansion, purchase acceleration, and repeat purchasing. The first four mechanisms relate to the immediate sales response, whereas the latter applies to the long-term (Narasimhan et al. 1996). In addition, promotional elasticities vary across categories. Narasimhan et al. (1996) report that categories with relatively fewer brands, higher penetration, shorter interpurchase times, and that are easy to stockpile are likely candidates for promotional activities, because they have high promotional elasticities. Price promotions, though highly effective in the short run, generate only weak, if any, impacts on long-run brand and category demand (e.g., Ailawadi et al. 2006; Nijs et al. 2001). Moreover, short- and long-term promotional effectiveness lessens with nonprice advertising (Nijs et al. 2001).

In Figure 2.1, we present the sales performance driver that we selected for further empirical analysis. The vertical pillars group the performance drivers into market and store characteristics, whereas the horizontal pillars indicate the hierarchical level on which they are measured. Before we discuss the analytical procedure in detail, we continue with the data description and measures in the next section.

Figure 2.1: Sales performance drivers



2.5 DATA AND MEASURES

In this section, we present the data and outline the variable measures of the study to identify the factors that might explain the performance of different pharmacy outlets in the Dutch market.

2.5.1 Data description

The study data come from 32 outlets of a Dutch retail pharmacy chain and include monthly category sales in three broad OTC product categories – skin care, vitamins and minerals, and self-care[8] – over a period of two years (2007–2008). The categories were chosen in cooperation with the retailer. According to the pharmacy chain, they form the three largest categories of products sold over the counter, accounting for more than 70 percent of its total OTC turnover. We gathered information on promotional activities during the study period, as well as the number of competitors in the four-digit zip code area (i.e., drugstores and pharmacies outside this chain). We also obtained store-specific and assortment-related characteristics from the retailer for each outlet. In addition, sociodemographic characteristics observed at the four-digit zip code level were available from a Dutch supplier of household data. Finally, a large customer survey provided additional information about how pharmacy patrons perceived the assortment and other store-specific factors in each outlet. The summary statistics are in Table 2.1.

2.5.2 Customer survey measures

To assess customers' perceptions of the store outlet and their propensity to buy on impulse, a survey of the pharmacy customers was conducted in cooperation with the pharmacy chain. The survey attributes examined were determined by screening past store image and impulse buying studies, a pilot test, and in agreement with the pharmacy chain. The individual pharmacy outlets distributed the questionnaires.

2.5.2.1 Store image assessment

Despite the widely accepted importance of store image in determining store patronage and thus sales performance, no unique conceptualization or operationalization of this concept exists, and its effect is still difficult to assess (Chowdhury et al. 1998; Kasulis and Lusch 1981). In all conceptualizations, the way customers perceive the store with respect to different salient attributes (not limited to physical attributes but also involving psychological ones) is the dominant theme (McGoldrick, 2002). To assess store image, we borrowed several items that

[8] The self-care category comprises products such as pain relievers, cold and cough products, and so on.

have been used by previous studies to capture the multifaceted store image construct (for a thorough summary, see Ailawadi and Keller 2004; McGoldrick 2002). The items covered topics such as convenience, merchandise assortment, in-store atmosphere, sales personnel, and promotions, adjusted to match the retail pharmacy context (see Appendix 2.1). We conducted a principal component analysis of the 11 items used to assess store image, which indicated two extracted factors that explained 59.4 percent of the variance. One factor captured the promotion dimension, and the other factor captured the remaining dimensions. Although store image literature subsumes these items into one construct, we retain the two-factor solution and label each as marketing evaluation (MktgEval) or store evaluation (StEval). Reliability scores for both marketing and store evaluation surpass the .70 threshold (.88 and .82, respectively). We aggregated these data across customers, to the pharmacy outlet level, before including them in our subsequent analysis.

Table 2.1: Means and standard deviations of selected store and category characteristics

Variables	Mean (SD)	Mean (SD) per Category		
		Skin Care	Vitamins/ Minerals	Self-Care
Sales (in Euro)	2227.85 [b] (1642.57)	2459.67 (1513.39)	697.13 (321.06)	3526.76 (1272.16)
Store size (m^2)	57.97 (24.47)			
Number of competing pharmacies and drugstores[a]	1.84 (1.69)			
Population density (per km^2)[a]	3157.72 (2784.87)			
'Isolated' pharmacy outlet (dummy variable)	0.31 (0.47)			
Number of added subcategories (in addition to the core category assortment)	0.94 (1.41)	0.75 (0.90)	0.19 (0.39)	1.88 (1.89)
Proneness to impulse purchasing	2.44 (0.21)	2.50 (0.20)	2.37 (0.23)	2.45 (0.19)
Promotional activity (dummy variable)	0.43 (0.50)	0.58 (0.49)	0.08 (0.28)	0.62 (0.48)

[a]Based on the four-digit zip code area.
[b]Average monthly store sales; this value indicates how much a pharmacy outlet sells on average per month in categories skin care, vitamins, and self-care.

2.5.2.2 Impulse proneness assessment

Drawing on previous definitions, we regard impulse proneness as a category characteristic. The impulse proneness assessment used items from existing impulse buying measurement scales (Narasimhan et al. 1996; Rook and Fisher 1995). We obtained these measures from survey respondents, who indicated their propensity to buy particular OTC categories on impulse. The calculated category-specific averages are used for the further analysis.

2.5.3 Remaining measures

We used category-specific sales as our criterion variable to assess a store's sales performance. To measure *competition*, we counted the number of drugstores and competing pharmacy outlets operating in the same four-digit zip code area as the pharmacy outlet. Information about whether a pharmacy outlet is situated in an area with more shops and/or facilities came from the retailer. We used an indicator variable to specify whether the outlet was 'isolated' or located in an area with several shops and/or facilities (*isolated*). The *inverse of population density* provided a proxy for average travel distance; in a densely populated area, the average customer travels less. To avoid scaling issues, we multiplied this value by 1000. The *size of the store* was measured by square meters. The sociodemographic control variables were determined by four factors, labeled 'senior citizens', 'upper class', 'non-Dutch', and 'single households'. We performed a principal component analysis that transformed the original variables into these four factors, because we suspected the original variables might be highly correlated (see Appendix 2.2).

The chain's core assortment remains the same across all outlets, but each store can supplement its core assortment with additional subcategories, such as specific weight-loss products that are not part of the core assortment of the self-care class. Therefore, we measured additional assortment as the number of individually added subcategories per product category (i.e., skin care, vitamins/minerals, and self-care).

Promotions are category specific and do not vary across outlets. Because we could not distinguish price from feature promotions, we defined a dummy variable indicating whether a category was on promotion in a certain month. We also accounted for post-promotional dips by incorporating the lagged promotional variable. That is, a temporary decrease in sales can occur if consumers accelerate their purchases and/or stockpile in response to a promotion and thus can refrain from later purchases (van Heerde et al. 2000). In line with previous findings (Macé and Neslin, 2004; van Heerde et al. 2004), we considered a one-month lag period. We summarize all these variables and their measurement in Table 2.2.

Table 2.2: Description of the dependent and independent variables

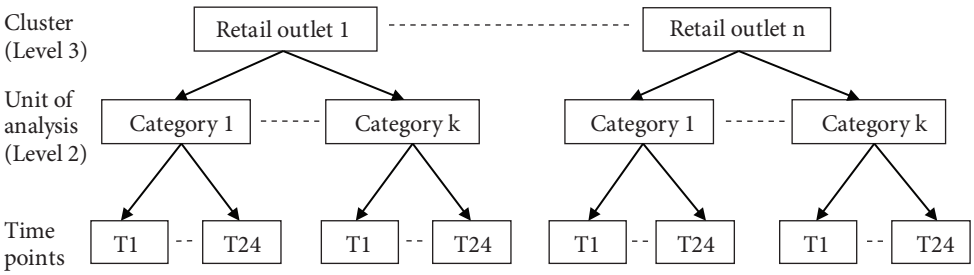
Variables	Description
Dependent variable:	
Sales	Sales performance, measured by (the logarithm of) the store's monthly category sales divided by store size
Independent variables:	
Store variables	
Comp	Number of competing pharmacies and drugstores[a)]
InvPopDensity	(Inverse of) population density (per km²)[a)]
Isolated	Location indicator specifying whether a pharmacy outlet is isolated
StEval	General valuation of the pharmacy outlet and its marketing activities (based on certain established store image items)
MktgEval	
SeniorCitizens	Areas with mature adults and families without children[a)]
Upper class	Areas with upper and upper middle class families[a)]
NonDutch	Multiracial areas with low income households[a)]
SingleHH	Areas with young adults and single households[a)]
Category variables	
AddAssort	Number of subcategories in addition to the core category assortment, corrected by store size
Impulse	Proneness to impulse purchasing (defined as category characteristic)
Within-category variables	
Trend	(logarithmic) Time trend
Promo	Promotional activity undertaken in a certain month (dummy variable)
$Promo_{t-1}$	Lagged promotional activity undertaken in a certain month

[a)]Based on the four-digit zip code area.

2.6 METHODOLOGY

In Figure 2.2, we illustrate the structure of the data we used in this study. Categories (our units of analysis) are nested within stores. We collected repeated measures of the units of analysis over time, representing the lowest level. This hierarchy is also visible in the data structure (see Figure 2.2).

Figure 2.2: Data structure used for the hierarchical linear model



To account for the multilevel data structure, we employed a hierarchical linear modeling (HLM) framework (Raudenbush and Bryk 2002). Before estimating the proposed model, we applied a logarithmic transformation to our dependent variable, sales per square meter.

The model features three levels of analysis. At Level 1, the dependent variable, category sales is determined by (1) an intercept that depicts the mean (sales) performance of category *i* from store *j*, (2) a time trend, (3) the promotion variable at occasion *t* and the lagged promotion variable, and (4) an error term. Thus, the Level 1 model is:

$$\text{Sales}_{ijt} = \pi_{0ij} + \pi_{1ij} \times \text{Trend}_{ijt} + \alpha_2 \times \text{Promo}_{it} + \alpha_3 \times \text{Promo}_{i,t-1} + e_{ijt} \tag{2.1}$$

where Sales_{ijt} refers to adjusted category sales, or the log-transformed category *i* sales per square meter of the store *j* in month *t*; Trend_{ijt} is a logarithmic time trend; and Promo_{it} is equal to 1 if category *i* was promoted in month *t* and 0 otherwise. The error term e_{ijt} is assumed to be normally distributed with mean 0 and variance σ^2.

At Level 2, the category-specific intercept π_{0ij} and trend slope π_{1ij} can be modeled as:

$$\begin{aligned} \pi_{0ij} &= \beta_{0j} + \beta_1 \times \text{AddAssort}_{ij} + \beta_2 \times \text{Impulse}_{ij} + r_{0ij} \\ \pi_{1ij} &= \gamma_1 + r_{1ij} \end{aligned} \tag{2.2}$$

where AddAssort_{ij} is the adjusted additional assortment, that is, the number of additional assortments in category *i* divided by the size of store *j*; and Impulse_{ij} is impulse proneness with respect to category *i* in store *j*. The random effect of the intercept r_{0ij} is assumed to be normally distributed over categories (within outlets), with an expected value of 0 and $\text{var}(r_{0ij}) = \tau_0^2$. By

including r_{1ij}, we specify a randomly varying trend that acknowledges that categories' growth trajectories, in terms of sales performance, can differ and are not fixed across categories. However, the random trend is not predicted by category or store variables. The random effect r_{1ij} that is associated with the trend coefficient is assumed to follow a normal distribution, with 0 mean and constant variance, $\text{var}(r_{1ij}) = \tau_1^2$.

Finally, at Level 3, the variation in category sales across pharmacy outlets is given by:

$$\begin{aligned}\beta_{0j} = {} & \delta_0 + \delta_1 \times \text{Comp}_j + \delta_2 \times \text{InvPopDensity}_j + \delta_3 \times \text{Isolated}_j + \delta_4 \times \text{StEval}_j \\ & + \delta_5 \times \text{MktgEval}_j + \delta_6 \times \text{SeniorCitizens}_j + \delta_7 \times \text{Upper class}_j + \delta_8 \times \text{NonDutch}_j \\ & + \delta_9 \times \text{SingleHH}_j + u_{00j}, \end{aligned} \tag{2.3}$$

where Comp_j refers to the number of competitors of pharmacy j; InvPopDensity_j is the inverse of population density in the zip code area of pharmacy j; Isolated_j equals 1 if pharmacy j is an isolated outlet and 0 otherwise; StEval_j, MktgEval_j denote the valuation of store image factors and marketing activities, respectively, for pharmacy j; and SeniorCitizens_j (Factor 1), Upper class_j (Factor 2), NonDutch_j (Factor 3), and SingleHH_j (Factor 4) are the sociodemographic control variables The random effect associated with the intercept for outlet j, u_{00j}, has a normal distribution with mean 0 and $\text{var}(u_{00j})=\varphi^2$. In Equations (2.1) and (2.2) we modeled α_2, α_3, β_1, β_2, and γ_1 as fixed coefficients. The likelihood ratio test indicates the insignificance of random store-specific slope coefficients.

By substituting Equations (2.2) and (2.3) into Equation (2.1), we obtain the full model:

$$\begin{aligned}\text{Sales}_{ijt} = {} & \delta_0 + \delta_1 \times \text{Comp}_j + \delta_2 \times \text{InvPopDensity}_j + \delta_3 \times \text{Isolated}_j + \delta_4 \times \text{StEval}_j \\ & + \delta_5 \times \text{MktgEval}_j + \delta_6 \times \text{SeniorCitizens}_j + \delta_7 \times \text{Upper class}_j + \delta_8 \times \text{NonDutch}_j \\ & + \delta_9 \times \text{SingleHH}_j + \beta_1 \times \text{AddAssort}_{ij} + \beta_2 \times \text{Impulse}_{ij} + \gamma_1 \times \text{Trend}_{ijt} \\ & + \alpha_2 \times \text{Promo}_{it} + \alpha_3 \times \text{Promo}_{i,t-1} + u_{00j} + r_{0ij} + r_{1ij} \times \text{Trend}_{ijt} + e_{ijt} \end{aligned} \tag{2.4}$$

2.7 RESULTS

By employing an iterative procedure to maximize the likelihood, our multilevel model approach can simultaneously estimate parameters at different levels.[9] We provide the results

[9] According to Hox (2002), maximum likelihood estimation is the most common method for estimating HLM. We used the restricted maximum likelihood algorithm to compute the coefficients of the predictor variables.

of the hierarchical linear model specification proposed in Equations (2.1)–(2.3) in Table 2.3; in the following sections, we discuss the outcomes in greater detail.

2.7.1 Level-3 effects

Competition in the trade area is significant at the 10 percent level. The positive coefficient suggests that sales performance is higher for stores in areas with more competitors, as also suggested by Campo et al. (2000) and Hunneman (2011). This somewhat counterintuitive result may arise because areas with higher economic potential are also more attractive for competitors (Campo et al. 2000). Individual stores can benefit from the close proximity of competitors, because consumers find it more attractive to visit that area and search and compare among stores (Gonzáles-Benito and Gonzáles-Benito 2005). With regard to location – a widely cited core element of retail store choice decisions and store performance – we find no significant effect, whether for the location indicator or the inverse density measure. Nor is marketing evaluation or store evaluation significant. These findings contrast sharply with existing findings that affirm the crucial role of location characteristics and image. Finally, the demographic control variables indicate no significant effects.

2.7.2 Level-2 effects

The effects of additional assortment and impulse proneness are significant and in line with existing literature. The number of added assortment items is highly significant and enhances sales performance. Furthermore, we observe a significant, positive influence of impulse proneness on category sales. The more customers engage in unplanned category purchases, the more beneficial it is for the (category) sales performance of the outlet.

2.7.3 Level-1 effects

As we show in Table 2.3, promotions have a significant and positive effect on (category) sales performance. The significant negative coefficient for the promotion variable at lag 1 implies a postpromotion dip, such that (category) sales in the period following the promotion decline. This temporary sales decrease likely results from purchase acceleration (e.g., van Heerde et al. 2000); that is, consumers decide to make a category purchase during the promotion period that they otherwise would have made in the future. The trend receives support.

Table 2.3: Estimated parameters of the hierarchical linear model

Independent Variables	Dependent Variable: ln (Sales/Store size)	
	Parameter Estimates[a]	Effect Size r[b]
Intercept	0.253 (1.265)	
Level 3: Store characteristics		
Comp	0.153 (0.079)*	0.43
InvPopDensity	-0.001 (0.097)	0.00
Isolated	-0.070 (0.286)	0.06
StEval	0.035 (0.337)	0.03
MktgEval	0.081(0.485)	0.04
Socio-demographics		
SeniorCitizens	0.215 (0.142)	0.33
Upper class	0.171 (0.130)	0.31
NonDutch	-0.003 (0.145)	0.01
SingleHH	0.074 (0.123)	0.15
Level 2: Category characteristics		
AddAssort	13.865 (3.945)**	0.36
Impulse	1.030 (0.497)**	0.24
Level 1: Within-category characteristics		
Trend	0.054 (0.026)**	0.21
Promo	0.092 (0.013)**	0.15
$Promo_{t-1}$	-0.033 (0.014)**	0.05

*p<.1; **p<.05

[a] Individual parameters are unstandardized, with standard errors in parentheses.

[b] The (absolute) effect size r is computed as $r = [t^2/(t^2+df)]^{0.5}$.

2.7.4 Importance of performance drivers

We are interested in factors with significant impacts on category sales performance, as well as in the magnitude of their effects. To assess the importance of the performance drivers we follow Steenkamp et al. (1999) and compute effect sizes on the basis of the *t*-values of the parameter estimates and the degrees of freedom, $r = [t^2/(t^2+df)]^{0.5}$.[10] The effect sizes appear in Column 3 of Table 2.3. In comparing the magnitude of effects of the various factors, we note in particular the key role of category characteristics: Additional assortment items have an (absolute) effect size of .36, and impulse proneness indicates an effect size of .24. Strategic

[10] The HLM method does not provide a straightforward way to report standardized coefficients or elasticities (Steenkamp et al. 1999).

planning about the assortment (i.e., category management) thus offers a promising method to increase sales performance. The effect of promotions is weaker, with a direct effect size of .15. Still, promotional activities are not negligible in terms of their ability to improve category sales. The effect size of promotions at lag 1 instead is rather small, implying a modest sales decrease.

2.7.5 Robustness checks

To examine whether multicollinearity may affect our model, we assess the bivariate correlations and variance inflation factors (VIF). As we show in Table 2.4, the bivariate correlations between the regressors are less than |.40| in 97 percent of the cases, and the VIF are all less than 2. Thus, multicollinearity does not appear to be a concern. We further check for non-normality and heteroscedasticity, but doing so does not lead to any changes in our estimation procedure.

Endogeneity might exist between store size and sales. To test for this source of bias, we considered a fixed effects specification, yet the number of parameters, observations, and variability in the data made it impossible to estimate such a model. Therefore, we chose not to use models in which we explained (the logarithm of) sales but did not account for store size. To accommodate the potential endogeneity problem, we divided sales by store size (van Dijk et al. 2004), and we also applied a similar division for the additional assortment variable.

We estimated the model including an additional location variable to measure the average distance to the closest general practitioner (GP), because customers might prefer pharmacy locations close to their GP. This inclusion did not improve the model. Including month dummies, to account for seasonality, and interaction terms between the demographic characteristics and the promotion variable did not reveal a clear seasonal pattern or a significant effect for the interaction terms. Overall, the results remained fairly stable across different model specifications.

Table 2.4: Bivariate correlations and VIF values

Variables		Bivariate correlation													VIF
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	
1.	Sales															
2.	Comp	.21														1.54
3.	InvDensity	-.01	-.16													1.35
4.	Isolated	.02	-.22	.04												1.55
5.	StEval	-.09	-.01	-.08	.10											1.41
6.	MktgEval	.09	.09	.08	-.03	.10										1.91
7.	SeniorCitizens	.17	-.05	.18	-.01	-18	.46									1.86
8.	Upper class	.08	-.23	.27	.47	-.14	-.12	.00								1.55
9.	NonDutch	.02	-.16	-.32	.29	.24	-.37	.01	-.00							1.96
10.	SingleHH	.18	.47	-.08	.05	.14	.07	.00	.00	-.00						1.38
11.	AddAssort	.27	-.04	-.01	.01	-.12	-.02	.09	-.04	.10	-.06					1.12
12.	Impulse	.08	-.13	-.18	.06	-.06	-.26	-.36	.05	.18	.01	.09				1.33
13.	Trend	.04	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00			1.04
14.	Promo	.38	.00	.00	.00	.00	.00	.00	.00	.00	.00	.19	.12	.22		1.21
15.	$Promo_{t-1}$	.36	.00	.00	.00	.00	.00	.00	.00	.00	.00	.20	.12	.17	.38	1.22

Notes: Correlations greater than |.04| are significant at $p<.05$ (two-tailed test).

2.8 DISCUSSION

Our study reveals that marketing mix factors (i.e., assortment and promotions) are essential determinants of retail pharmacies' ability to generate category sales increases and improve their performance. Specifically, additions to a (core) assortment have notable positive impacts on category sales performance. We thus confirm the central role of a retailer's product assortment decisions (see Mantrala et al. 2009).

Our findings further demonstrate that offering (sub)categories that tend to provoke impulse buying provide opportunities for pharmacies to increase their sales and thus constitute a potential additional revenue source. A UK study has shown that only 57 percent of all OTC purchases are entirely preplanned; in 23 percent of the cases, the customer anticipates a need, but the actual purchase decision takes place in the store. In the remaining 20 percent of purchases, the choices depend on influences in the store (McGoldrick 1982). Despite key differences across OTC categories, the outcomes underline the value of selective merchandising stimuli, including displays and other in-store influences, for pharmacy outlets.

Promotions offer an effective means of enhancing (short-term) performance; unlike in the prescription drug market, they are permitted for OTC drugs. Promotions increase the visibility of the outlet's (promoted) products and services and of the outlet itself, thus providing an opportunity for pharmacies to become more attractive to existing and potential customers.

In contrast with the conventional wisdom though, we find that market/location characteristics (cf. competition) play rather insignificant roles in the retail pharmacy market. Our findings reject the relevance of location and store factors as performance drivers (e.g., Baker et al. 2002). Prior research that emphasizes their relevance mainly has focused on grocery retailers and convenience goods; perhaps our contrasting findings emerge because for medical products, which invoke high personal involvement, factors such as reputation or competency, rather than convenience for example, determine store choice (Franic et al. 2008). Prior literature confirms that for important product categories or those perceived as risky, customers often prefer specialty stores (Dash et al. 1976). Another possible explanation could be forced loyalty: In many rural areas, there is only one pharmacy outlet. Elderly or less mobile people thus may have no choice other than to visit this outlet. Customer experiences in the pre- and postpurchase phases go beyond the store's environmental elements to include social elements (e.g., others' influence) and the purpose of the shopping trip (Verhoef et al. 2009). Because OTC products are experience (or even credence) goods, these latter elements likely dominate, which might explain our seemingly surprising finding that the customer's

store perceptions had no significant influence on pharmacy sales performance. An alternative explanation may be that customers who visit a pharmacy are driven by utilitarian rather than hedonic values. Accordingly, pharmacy patrons' intentions to purchase OTC products will be less affected by store image cues than by the pharmacy staff's expertise and advice (Guido et al. 2011).

2.9 CONCLUSIONS AND DIRECTIONS FOR FURTHER RESEARCH

This chapter contributes to retailing literature in several ways. On the conceptual side, this analysis highlights retail pharmacies, an increasingly important but sparsely investigated player in the healthcare market. Such findings are relevant not only in a Dutch context but also for other countries that have recently deregulated their retail pharmacy sector or started to do so. The findings offer insights into the critical performance drivers and how to exploit them efficiently. From a managerial perspective, the results of our analysis can help retail pharmacies better understand the benefits of adopting a strategic retail marketing focus. In practice, we observe that many retail pharmacies have not yet recognized the full potential of their strategic marketing mix activities, and their marketing and retail skills appear poorly developed. Pharmacists still see themselves as healthcare or therapeutic experts first and retailers second (Schmidt and Pioch 2004). However, developments in the healthcare market demand a strategic change by retail pharmacies if they hope to outperform their competitors. Such competitive advantages will arise from a combination of professional healthcare information, including advice on drug choice and usage, with attractive and well-communicated propositions for customers. Finally, our results can inform retailers in other recently deregulated markets, such as energy or telecommunications.[11]

Our study also suffers some limitations that provide opportunities for ongoing research. First, we studied only one chain in one country. Pharmacy markets and their corresponding regulations differ across countries; therefore, it would be interesting to test our model in other countries. Our results provide a basis for understanding how to deal with the effects that changing healthcare markets will have on retail pharmacies in most countries. Second, we use a general promotion variable, such that we cannot disentangle which activities – price discounts, features, displays – are most effective for enhancing category sales. Nevertheless, the finding that promotional activities have significant performance impacts

[11] Wieringa and Verhoef (2007) investigate customer switching in the liberalized Dutch energy market.

already is a surprising and helpful insight for retail pharmacists. Third, we had limited control over the distribution of the survey, due to the indirect dissemination of the questionnaires, which were handed out exclusively to existing pharmacy customers. This distribution may introduce a selection bias. However, if such an effect existed, it would apply to all respondents and thus exert only a minimal influence on the outcomes of our analysis regarding differences between stores. Fourth, the deregulation of the healthcare market in the Netherlands is not yet complete. Our study offers a first attempt to provide insights into the specific challenges of a deregulated pharmacy market, but clearly, more research is needed to capture other potentially relevant performance drivers. Ongoing exploration of additional variables, such as those related to customer relationship management and customer experience (Verhoef et al. 2009), could generate more valuable insights. Deregulation is a common phenomenon in many countries and across industries (e.g., energy, telecommunication); it would be interesting to analyze how consumers and firms react to deregulated markets over time.

APPENDIX 2.1: MEASUREMENT ITEMS

Table A1: Items used and results of the principal component analysis for store image

	Description	Factor 1 StEval	Factor 2 MktgEval
1.	How satisfied are you with the accessibility of the pharmacy?	.559	-.030
2.	The in-store information influences my purchase decisions	.623	.083
3.	The in-store information is informative	.759	.124
4.	The pharmacy has a pleasant atmosphere	.780	.198
5.	I can easily find the products I am looking for	.707	.219
6.	The assortment of the pharmacy offers much variety	.605	.221
7.	In general, I am very satisfied with the personnel of the pharmacy	.700	.215
8.	In general, I am very satisfied with the service the pharmacy provides	.721	.237
9.	How do you evaluate the pharmacy's seasonal brochure?	.171	.867
10.	How do you evaluate the pharmacy's direct mailings?	.176	.891
11.	How do you evaluate the pharmacy's promotional offers?	.174	.891
	Cumulative percentage of variance explained	35.02	58.65
	Reliability (α)	.85	.89

Notes: Item 1 is rated on a five-point scale, from very unsatisfied (1) to very satisfied (5). Items 2–8 are rated on a five-point scale, ranging from completely disagree (1) to completely agree (5). Items 9–11 are rated on a scale from 1 to 10 (1 = very negative; 10 = very positive). All items are translated from Dutch. The attributes for the pharmacy outlet evaluation with regard to selling over-the-counter medication were based on established scales. Items 1–5 and 9–11 were adapted to our study context from previous store-image research (Chowdhury et al. 1998; McGoldrick 2002; Westbrook 1981). Assortment item 6 came from Broniarczyk et al. (1998); the service items (7, 8) came from Parasuraman et al. (1985).

Table A2: Items used for impulse proneness

	Description
1.	I sometimes buy a product of category X without having planned beforehand
2.	I carefully plan most of my purchases in category X$^{(*)}$

Notes: We consider a category-specific impulse proneness measure (cf. Narasimhan et al. 1996). Both items were adapted from Rook and Fisher (1995) for the study context. The items were rated on a five-point scale, ranging from completely disagree (1) to completely agree (5). $^{(*)}$ Reverse coded.

APPENDIX 2.2: SOCIODEMOGRAPHIC VARIABLES

Table A3: Principal component analysis

Description	Component			
	1 Senior citizens	2 Upper Class	3 Non Dutch	4 SingleHH
% single people, < 35 years	-.528	-.422	.315	.617
% single people, 35-55 years	-.477	-.330	.555	.319
% single people, > 55 years	.865	-.190	-.014	.266
% families without children	.593	.340	-.639	.115
% families with children	-.265	.370	-.014	-.877
% single households	-.117	-.529	.425	.701
% two-person households	.548	.208	-.643	.135
% three-person households	-.148	-.119	.108	-.875
% households with four or more persons	-.163	.637	-.210	-.615
% principal wage earner under 25 years of age	-.603	-.304	.320	.449
% principal wage earner between 25 and 45 years of age	-.873	-.247	.304	-.132
% principal wage earner between 45 and 65 years of age	.547	.664	-.161	-.161
% principal wage earner above 65 years	.852	-.174	-.347	.150
% Dutch origin	.310	.257	-.865	-.040
% Western origin[a)]	.088	.115	.797	.298
% Non-western origin[b)]	-.383	-.324	.749	-.056
% with (gross) income below 32,000 Euro p.a.	-.312	-.830	.172	.296
% with (gross) income between 32,000 and 64,000 p.a.	.595	.577	-.131	-.362
% with (gross) income 80,000 p.a. and more	-.198	.827	-.145	-.004
Cumulative % of variance explained	25.95	46.12	66.22	85.01

[a)]Western origin includes European countries, North America, Oceania, Indonesia, and Japan.
[b)]Non-western origin includes Turkey, Africa, Latin-America, and Asia (cf. Indonesia and Japan).
Notes: The variables in Column 1 depict sociodemographic characteristics of the population of each store's four-digit zip code area. The principal component analysis, based on the latent root criterion, resulted in a solution with four factors. These four factors explained 85% of the total variation. Columns 2–5 show the factor loadings obtained after a Varimax rotation. Underlined values have the strongest relationship with the respective factor.

Part II

Chapter 3

Impact of safety-related regulatory action on drug use in ambulatory care in the Netherlands*

3.1 INTRODUCTION

At market entry, the safety profile of a new drug is not fully known because of inherent shortcomings of preregistration clinical trials, such as small sample sizes, focus on efficacy, and inclusion of relatively healthy patient groups (Califf 2007; Stricker and Psaty 2004). For approximately 10% of all drugs, new and serious safety issues are identified after market approval, necessitating safety-related regulatory action (Heemstra et al. 2010; Lasser et al. 2002; Mol et al. 2010). These safety issues can emerge not only shortly after market entry but also at a later stage in the drug's life cycle (Mol et al. 2010). Occasionally, the benefits of a drug no longer outweigh its risks, leading to its withdrawal from the market. For example, rimonabant, an antiobesity drug, was withdrawn in 2009 because of safety concerns at an early stage of its life cycle (<3 years after market approval). Similarly, rosiglitazone, a drug used to treat diabetes, was withdrawn in 2010 at a more mature stage (> 10 years after market approval; EMA 2009, 2010). Ongoing postregistration benefit-risk evaluation and, when indicated, safety-related regulatory action are required to safeguard a positive balance of benefits over risks of individual drugs. To this end, risk management plans became mandatory in the European Union in 2005 (Raine et al. 2011).

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Prescribing trends of drugs presumably show an initial increase in prescription rates, after which they level out, and at a later stage in the life cycle they decrease (Leeflang and Wieringa 2010). One would expect safety-related regulatory action to have dissimilar impact, depending on when in the drug's life cycle it is taken. However, such information is currently not available.

Communication of important new safety issues in the European Union is currently primarily performed by sending paper-based warning letters to healthcare providers; these are called Direct Healthcare Professional Communications (DHPCs or 'Dear Doctor Letters'). DHPCs in the European Union are defined as information aimed at ensuring safe and effective use of medicinal products (EC 2008). In recent years, the effectiveness of these warning letters has been questioned (Goldman 2004; Woosley 2000; Yu et al. 2011). The impact of safety-related regulatory action was evaluated mainly for third generation oral contraceptives, cisapride and selective serotonin reuptake inhibitors (De Vries et al. 1998; Morrato et al. 2008; Smalley et al. 2000; Weatherby et al. 2001; Wheeler et al. 2008; Williams et al. 1998). The small number of drug groups, often weak study designs, and differences in outcome measures hamper drawing conclusions on effect sizes of safety-related regulatory action. Information about the impact of DHPCs is particularly relevant because evaluating the outcome of risk minimization will become mandatory in the near future and a point of reference is needed (Directive 2010/84/EU; Regulation (EU) No 1235/2010).

The aim of this study is to evaluate the impact of DHPCs on drug use in the Netherlands, taking into account preexisting prescribing trends.

3.2 METHODS

3.2.1 Design

In this longitudinal study, all drugs for which a DHPC was issued between January 2001 and January 2008 in the Netherlands were included. We excluded drugs that were not dispensed in ambulatory care, drugs that had insufficient dispensing data (≤ 10 Rx/month pre-and post-DHPC), and drugs for which a market withdrawal was announced in the DHPC.

New drug use (defined as number of new prescriptions per drug and no dispensing to the patient in the previous six months) was selected as main outcome measure to assess the impact of DHPCs. The following drug and DHPC characteristics were retrieved: International Nonproprietary Names (INN), ATC classification, registration date, date of DHPC, time from registration to DHPC, and safety issue (including System Organ Class).

3.2.2 Data

Monthly dispensing data for the period 2000-2008 was obtained from the Dutch Foundation for Pharmaceutical Statistics database. This database comprises drug dispensing data of about 90% (15 million) of the Dutch population (SFK 2010). DHPCs were collected from the Dutch Healthcare Inspectorate paper archive and the website of the Dutch Medicines Evaluation Board (MEB). The drug and DHPC characteristics were retrieved from the DHPCs, the Database Human Medicines of the Dutch Medicines Evaluation Board, the World Health Organization ATC classification system (WHO 2010), and the Medical Dictionary for Regulatory Activities.

3.2.3 Analyses

The DHPC is used as the unit of analysis. We first evaluate the impact of DHPCs on short-term volume of drug use using regression models. Second, we determine whether a DHPC led to a long-term change in use with interrupted time series analyses.

3.2.3.1 Short-term changes in volume of use

Short-term changes in use were defined as a significant increase, no change, or a significant decrease in prescription rates. Two aspects of change were identified: changes in average use (i.e., level) and trends in use (i.e., slopes) before and after the DHPC. Per DHPC, we computed trend regression models for the periods 12 months before and 12 months after the DHPC. A pooled (two sample) *t*-test was used to determine whether the intercept estimates for the pre- and post-DHPC period were significantly different from each other. To consider all possible combinations in trend before and after the DHPC, we tested whether the estimates of the slope coefficient (for the pre- and post-DHPC period) were significantly different from zero, negative or positive. For that purpose, we performed standard *t*-tests. P-values of ≤ 0.05 were considered statistically significant.

3.2.3.2 Long-term changes in volume of use

We used an interrupted time series design based on the autoregressive integrated moving average (ARIMA) modeling approach to analyze the size and significance of long-term changes in use during the total study period associated with the DHPC for each drug included (Box and Tiao 1975; McDowall et al. 1980). Long-term changes indicate a change in the level of use from the time of the DHPC until the end of our observational period.

Safety-related regulatory action in the form of a DHPC is included in the model as an intervention that may interrupt the normal course of the use of a drug. We expected

a DHPC to have a sudden (rather than gradual) effect on drug use; therefore, we modeled the intervention as an abrupt change at the time of the DHPC that will have a permanent effect on drug use. The DHPC was included as a dummy variable taking the value 0 in the pre-intervention period and the value 1 at the time of intervention and thereafter. Because a DHPC could have been surrounded by premonition (e.g., scientific articles, communication circulated by healthcare professionals) or issued at the end of a month, we also allowed for a lead (i.e., the month before the issuance month) or delayed effect (i.e., one or two month after the DHPC) of the DHPC on the prescription series.

We determined an appropriate time series regression model that accounts for any (systematic) variation that is independent of the intervention. Plots of the raw data and the (partial) autocorrelation function were used to identify nonstationarity. In addition, unit root tests were applied. If nonstationarity was present, we transformed the series by taking first differences to yield a stationary series. On the basis of the partial autocorrelation function, we determined the order of the autoregressive and moving average components. Both seasonal fluctuations and trends were taken into account. The model with the best fit and adequate diagnostic statistics was chosen according to Akaike and Schwarz information criteria (Akaike 1974; Schwarz 1978). Residuals were computed for diagnostic checks.

To assess the impact of the intervention, the intervention term was inserted into the previously determined time series model. Changes in the level of prescribing (drug use) related to the intervention were considered statistically significant when $p \leq 0.05$.

The analyses were performed separately for each drug. When two DHPCs were issued close in time, they were treated as a single intervention and analyzed together. In such a case, the date of issuance of the first DHPC was taken as the time point of intervention.

To make the size of the impact comparable across drugs, we calculated standardized effect sizes by dividing the effect size by the median drug use in the 12 months before the intervention.

Chi-squares tests were used to assess associations between preexisting trends and long-term changes in use.

3.3 RESULTS

A total of 120 DHPCs were issued in the Netherlands during the study period. Sixty-one DHPCs were excluded from further analysis: 38 DHPCs were issued for drugs solely used in hospital settings, 18 DHPCs were issued for drugs with fewer than (median) 10 drug users

per month over the whole study period, and five DHPCs were issued for drugs that were withdrawn from the market. As a result, 59 DHPCs are included for 46 drug groups covering 11 of 14 Anatomical Therapeutic Chemical (ATC) groups (level 1). The impact of two DHPCs, both issued for nelfinavir one month apart, could not be evaluated separately and were therefore analyzed as one, leading to a total of 58 DHPCs to be analyzed for 46 drugs. DHPCs are issued after a mean of 9.67 (SD: 8.3) years after registration ('time from registration to DHPC'). In the 12-month (baseline) period preceding the DHPC, the median number of users of the included drugs ranges from 7 (sirolimus) to 53,596 (salbutamol) (Appendix 3.1).

3.3.1 Short-term changes in volume of use

Half (29) of all DHPCs were issued for drugs without any significant change in preexistent trends (slope) in use, 13 were issued for drugs whose use was decreasing, and 16 for drugs whose use was increasing in the 12-month period before the DHPC was issued (Table 3.1). The short-term level of prescribing is lower after the DHPC for half (28) of the drugs and evenly distributed across the unchanged (14) or higher (16) categories for the other half of the drugs. Three clusters in short-term changes in use exist. The first cluster consists of 11 of 13 drugs with decreasing use before the DHPC that continued to decrease or leveled off after the DHPC, but at a lower level than before the DHPC. A second cluster consists of 21 of 29 drugs with unchanged slope coefficients before and after the DHPC and with no changes in levels of use. The third cluster consists of eight drugs for which preexistent increasing use levels off after the DHPC but at a higher level than before the DHPC.

3.3.2 Long-term changes in volume of use

Forty-six interrupted time series models are developed to evaluate any long-term change in number of prescriptions after (58) individual DHPCs issued for the 46 drugs. Twenty (34.5%) DHPCs result in a long-term change in drug use (Appendix 3.1). For these 20 DHPCs, the mean use decreases by 26.7% (95% CI: -15.21% to -38.19 %). A long-term increase in use (+15.4%, 95% CI: 3.74% to 27.06%) is observed after the DHPC for lopinavir/ritonavir (Figure 3.1).

Table 3.1: Short-term changes in drug use pre-and post-DHPC (n=58)

Changes in trend*		Changes in level#		
Pre-DHPC	**Post-DHPC**	**Lower** (n=28)	**Unchanged** (n=14)	**Higher** (n=16)
Decrease (-) (n=13)	-	cisapride[1], cisapride[2], itraconazol, piroxicam, rosiglitazone[2]	––	––
	0	didanosine, gemfibrozil, HRT, leflunomide, desogestrel+EE, gestodene+EE	tenofovir[1]	––
	+	pimecrolimus	––	––
Unchanged (0) (n=29)	-	celecoxib[2], etoricoxib, rosiglitazone[1], stavudine	paroxetine[1]	––
	0	bupropion, lamotrigine[2], nelfinavir[1+2], pergolide, pioglitazone, repaglinide, somatropin, vigabatrine	hydroxycarbamide, imatinib mesilate[2], lopinavir+ritonavir[2], mycophenolate mofetil, nevirapine, rosuvastatin, salbutamol, triamcinolone acetonide	lopinavir+ritonavir[1], sirolimus, tamsulosine, topiramate, venlafaxine
	+	––	tacrolimus	sibutramine, tenofovir[3]
Increase (+) (n=16)	-	celecoxib[1]	tenofovir[4]	––
	0	paroxetine[2]	olanzapine	epoetin alfa[2], galantamine, imatinib mesilate[1], lamotrigine[1], letrozole, levetiracetam
	+	botulin A toxin, strontium ranelate	epoetin alfa[3]	epoetin alfa[1], etanercept, tenofovir[2]

Legend: Drugs with more than one DHPC are indicated by their number: '#'.

* Short-term changes in trend 12 months pre and post-DHPC, are indicated by 'decrease (-)' or, 'increase (+)' ($p < .05$), or by 'unchanged (0)' ($p \geq .05$).

Short-term changes in mean level 12 months post-DHPC compared to 12 months pre-DHPC, are indicated by 'lower' or 'higher' ($p < .05$) or unchanged ($p \geq .05$).

Example: cisapride[1] situated in the upper left cell, indicates that before the first DHPC of cisapride its short-term use was decreasing (changes in trend pre-DHPC) and continued to decrease after (post-DHPC) the DHPC. In addition, the level of use was lower after the DHPC. **DHPC**: Direct Healthcare Professional Communication; **HRT**: Hormone Replacement Therapy; **EE**: Ethinylestradiol.

3.3.3 Long-term changes in volume of use in relation to pre-existing prescribing trends

Significant long-term changes are seen in 8 of 13 (62%) drugs with a preexisting decreasing trend in use (cisapride[1], itraconazol, piroxicam, rosiglitazone[2], didanosine, lefunomide, desogestrel + ethinylestradiol and gestodene + ethinylestradiol), in 8 of 29 (28%) drugs with a stable (no significant increase or decrease) preexisting trend (etoricoxib, rosiglitazone[1], bupropion, lamotrigine[2], pergolide, pioglitazone, vigabatrine, and lopinavir + ritonavir), and in 4 of 16 (25%) drugs with a preexisting increasing trend (celecoxib[1], paroxetine[2], strontium ranelate, and olanzapine) (Table 3.1)[12]. However, no significant association is found between preexisting trends in use and significant long-term changes (χ^2=5.46; p=.065).

Almost all (18 of 20) DHPCs leading to long-term changes in drug use have a lower level of use in the short-term (12 months), whereas the DHPC for lopinavir/ritonavir (reporting a switch from capsule to tablet formulation) shows both a long-term increase in use and a higher use in the short-term. The impact of the DHPC for olanzapine is characterized by a short-term flattening off of use (increasing slope pre-DHPC and no significant (from null) change in slope post-DHPC), resulting in no significant short-term change in the level of use, but a significant long-term decrease in use post-DHPC.

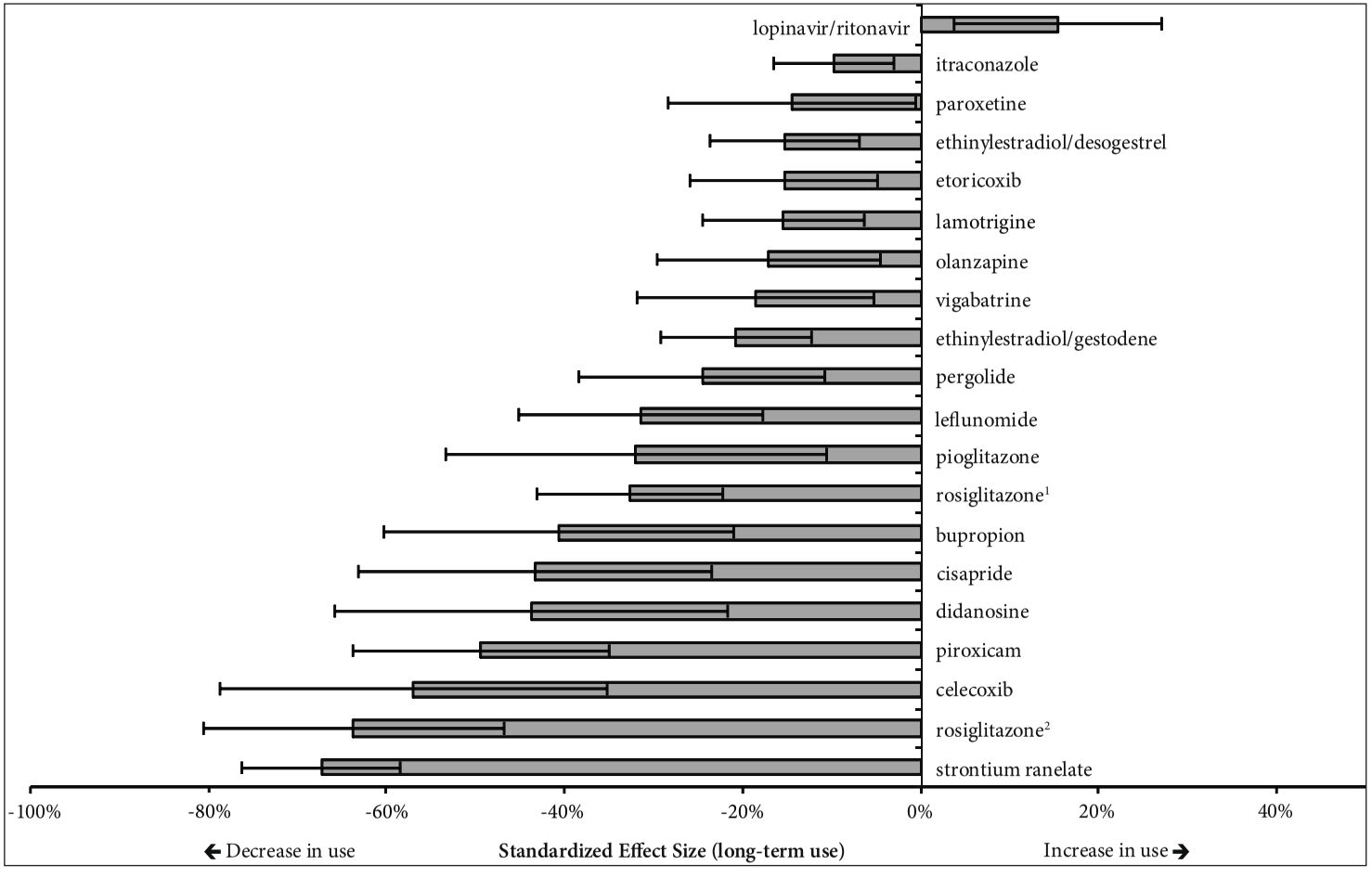
3.4 DISCUSSION

This study is the first to systematically assess the effects of safety-related regulatory action on changes in volume of drug use in ambulatory care over an extended period. In the short-term, almost half of all drugs with a DHPC show a decrease in use in the year after the DHPC was issued compared with the year before. Long-term changes in use are observed for a third of the drugs with a DHPC, resulting in a mean decrease of 26.7% in drug use, ranging from -10% to -67%. Changes in use are not clearly related to preexistent trends in use.

This study shows that DHPCs can lead to a considerable decrease in use of a minority of drugs. The results support earlier reported variation in the effect of safety-related regulatory action. Large reductions in use of coxibs in favor of nonsteroidal anti-inflammatory drugs (NSAIDS) were reported earlier in Germany (Schüssel and Schulz 2006), and large reductions in use of glitazones have been reported in the United States (Starner et al. 2008). Similar to our study, smaller or no decreases in drug use have been reported as well. A decrease of only 20%

[12] Drugs with more than one DHPC are indicated here by superscript numbers.

Figure 3.1: Standardized effect sizes of DHPCs leading to significant long-term changes in volume of new drug use



Legend: Drugs with more than one DHPC are indicated by their number: '#'

in overall antipsychotic drug prescriptions to patients with dementia was reported (Valiyeva et al. 2008). Use of isotretinoin did not decrease significantly after a DHPC informing healthcare providers about risk of psychiatric problems (Azoulay et al. 2006).

Several factors might explain the observed decreases in the use of drugs after a DHPC. For example, the observed decreases in use of the coxibs, pergolide, anti-HIV drugs, and bupropion may be explained by the availability of alternative drugs with a more favorable benefit-risk profile (Table 3.2). Moreover, in the Netherlands, bupropion is also indicated to assist patients in their wish to give up smoking and could therefore be considered a luxury drug, with limited medical need and a low acceptance of drug risks. The severity of the reported adverse drug events, e.g., strontium ranelate (Drug Rash with Eosinophilia Systemic Symptoms, DRESS), the coxibs (cardiovascular risk), glitazones (fracture risk), pergolide (cardiac valve disease), cisapride (QT prolongation), olanzapine (death), and vigabatrine (visual field defects) may explain the significant impact of the related DHPCs on drug use. The second DHPCs for both lamotrigine and paroxetine warned of potential teratogenic effects, which may be considered severe. However, these affect only a distinct subpopulation of women of childbearing age. The observed 15% (lamotrigine) and 16% (paroxetine) decreases in use may thus have been attenuated by evaluating the impact of the DHPCs on overall use, instead of use by this specific group of women alone.

Remarkably, the first DHPC for lopinavir/ritonavir leads to increased use, over both the long and the short-term. This may be explained by the message of the DHPC, which announced a switch from a capsule to a tablet formulation, which was intended to prevent a safety issue and thus not expected to cause a decrease in prescription rates. Moreover, prescribing of lopinavir/ritonavir is highly valued by many specialists because of the effectiveness of this combination in lowering patients' viral load (Croxtall and Perry 2010).

Of note, two-thirds of the DHPCs do not result in long-term changes in drug use. Factors that may explain the absence of long-term changes in our study are a lack of available alternative drugs, as in the case of etanercept, gemfibrozil, hydroxycarbamide, and imatinib (Table 3.2). The high medical need for these drugs in specific populations could overrule concerns prescribers may have with the reported safety issues in the DHPC. A number of DHPCs reported safety issues that were either already known or not unexpected from the underlying mechanism of action; for example, the second DHPCs for celecoxib and cisapride, hormone replacement therapy (breast cancer risk was widely published before the DHPC was issued; Faber et al. 2005), sibutramine (potential cardiovascular risk was already known at the time of approval), and pimecrolimus and tacrolimus (immune-modulating agents and risk of lymphomas). In these cases, physicians may have realized the risk associated with

these drugs earlier and adapted their prescribing behavior accordingly. Some adverse drug events may be rare and considered acceptable risks in the specific populations these drugs are used in, as in the case of tamsulosine (floppy-iris syndrome in the elderly patient) and hydroxycarbamide (cutaneous vasculitis in patients with cancer). Prescription of drugs such as epoetin alfa, imatinib mesilate, and levetiracetam is usually initiated by specialists and subsequently continued in ambulatory care. Specialists make more use of resources such as laboratory tests in comparison to general practitioners, facilitating continued use of drugs with a safety warning (Harrold et al. 1999). DHPCs related to off-label use could be another reason for the absence of a long-term effect. In such a case, the drug in question is often prescribed only to a small group of patients outside the regular indication. This could explain the lack of long-term impact of DHPCs for botulin toxin, galantamine, and letrozole. The DHPCs for levetiracetam, lopinavir/ritonavir[2], nelfinavir[1,2], repaglinide, and somatropin were issued to prevent medication errors (including drug-drug interactions). For example, in the DHPC for somatropin, defective calculators were called back that were distributed to prescribers to facilitate dose calculation of the growth hormone.

Half of all included drugs have a decrease in use in the year after the DHPC was issued. For eight of thirteen drugs with a declining use in the year preceding the DHPC, a long-term change in use is observed. This indicates an accelerating effect of the DHPC on already decreasing use of drugs that might be at the end of their lifecycle. Although we cannot confirm that older drugs more often showed declining use, at the mature stage of a product's lifecycle several alternative agents have usually become available. It is likely that the DHPC confirmed already existing doubts of prescribers about the safety of some of these drugs (cisapride, combinations of desogestrel and gestodene with ethinylestradiol, piroxicam), which made them stop prescribing the drugs to new patients. In the cases of cisapride-related cardiac arrhythmias and venous thrombosis related to combinations of desogestrel and gestodene with ethinylestradiol, the safety issues had already been described in the literature (Jick et al. 1995; Wysowski and Bacsanyi 1996), whereas the DHPC followed some time afterward (CBG-MEB 2011). A similar pattern is observed for piroxicam; its use had decreased before the DHPC was issued because of gastrointestinal complications. Nevertheless, we cannot conclude that a preexistent declining use is an established factor predicting the effectiveness of a DHPC because we do not observe a statistically significant association.

Further research is needed to determine the impact of the different factors discussed on the effect of DHPCs on use of individual drugs. Such knowledge can help optimize the impact of DHPCs.

Table 3.2: Potential explanations for (lack of) impact of DHPCs on volume of drug use

DHPCs with long-term changes (decrease in Rx) in use	
Alternative treatment available	bupropion, celecoxib[1], didanosine, etoricoxib, itraconazole, pergolide, stavudine
Limited medical need	Bupropion
Severe (new) ADE, including teratogenicity	celecoxib[1], cisapride[1], etoricoxib, itraconazole, lamotrigine[2], leflunomide, olanzapine, paroxetine[2], pergolide, pioglitazone, rosiglitazone[1, 2], strontium ranelate, vigabatrine
Confirmation of existing doubts/ Accelerating effect on decreasing drug use at end of its lifecycle	cisapride[1], combinations of desogestrel and gestodene with ethinylestradiol, piroxicam
DHPC with long-term change (increase in Rx) in use	
High medical need	lopinavir/ritanovir[1]
DHPCs without long-term changes in use	
No alternative treatment available/ high medical need	etanercept, gemfibrozil, hydroxycarbamide, imatinib mesilate
Known ADE	celecoxib[2], cisapride[2], etanercept, HRT, lamotrigine[1], mycophenolate mofetil, nevirapine, pimecrolimus, rosuvastatin, sibutramine, tacrolimus, tamsulosine
Rare ADE	tamsulosine, hydroxycarbamide
Specialist initiates drug therapy	epoetin alfa[1, 2, 3], imatinib mesilate[1, 2], levetiracetam, lopinavir/ ritonavir[2], mycophenolate mofetil, nelfinavir[1, 2], pimecrolimus, sirolimus, stavudine, tacrolimus, tenofovir[1 - 4], topiramate
Off label use	botulin a toxin, galantamine hydrobromide, letrozole, salbutamol, triamcinolon acetonide, venlafaxine
(Preventing) Medication error	levetiracetam, lopinavir/ritanovir[2], nelfinavir[1, 2], repaglinide, somatropin

Legend: Several explanations for (absence of) impact of a DHPC for a drug are possible. Drugs with more than one DHPC are indicated by their number: '#'. **ADE**: Adverse drug event; **DHPC**: Direct Healthcare Professional Communication; **HRT**: Hormone Replacement Therapy; **Rx**: Medical prescription.

3.4.1 Strengths and limitations

Our study expands the limited evidence that currently exists in literature of the impact of DHPCs. Our study includes DHPCs issued over a period of eight years and a wide range of safety issues representing all main therapeutic classes (ATC) prescribed in ambulatory care. Because the same method is used to assess the impact of DHPCs issued for a wide range of drugs, our results enable the comparison of effects of the different DHPCs. Our study could serve as a starting point for future research aimed at evaluating the impact of safety-related regulatory action.

In our study, we focus on the volume of new drug use as an outcome measure, instead of overall drug use. We assume new drug use to be more sensitive to changes in prescribing and therefore more responsive to the impact of safety-related regulatory action. The impact of DHPCs can also be analyzed using outcome measures that are directly attuned to the safety issue, for example, occurrence of the adverse event itself (Motola et al. 2008) or how often healthcare professionals perform recommended laboratory tests to identify early potential drug toxicity (Willy et al. 2002). These effects remain to be explored further in new studies.

We combine trend regression analysis for short-term evaluation of usage patterns with time series analyses to assess long-term changes in use. Time series analyses account for potential biases in the effect estimate of the intervention, such as secular trends, cyclical effects, random fluctuations, and correlation of adjacent error terms. This affords greater reliability of the measurement than before-after comparisons or linear regression (Wagner et al. 2002). Although suitable in the short-term, linear regression models cannot appropriately account for possible dependencies among observations over time. The combination of the two strategies allows for a clearer understanding of the impact of a DHPC.

A limitation of our study is that we do not have information on possible concomitant interventions that may have occurred at the same time. However, long-term changes affecting all DHPCs are unlikely given the heterogeneity in the drugs under study and the diverse timing of issuance of the DHPCs. In addition, our study has no control group, because legal requirements specify that DHPCs be sent to all relevant Dutch healthcare professionals. However, interrupted time series analysis is the most appropriate method to study intervention effects when it is not feasible to define a comparison group (Eccles et al. 2003). Moreover, we evaluate the impact of DHPCs only in the Netherlands. Healthcare professionals in other countries may respond differently to DHPCs. Similar analyses conducted in other countries would be an interesting route for further research.

3.4.2 Conclusion and recommendation

In conclusion, once safety issues for drugs are identified that warrant strong regulatory action, i.e., DHPCs, these result in substantial long-term reductions in use of only a third of issued DHPCs, independent of preexisting trends in use. The reason for less impact could be due to factors such as the type of adverse drug event, availability of alternative agents, and the type of prescriber. Our current understanding of the influence of these factors is still limited and further research is needed to complement findings from this study, and methods to enhance the impact of DHPCs should be explored.

The next chapter builds on the findings and discussion presented here, and explores the impact of drug and DHPC related characteristics on the effect of DHPCs on drug use.

APPENDIX 3.1: CHARACTERISTICS OF DHPCS WITH AND WITHOUT LONG-TERM IMPACT ON DRUG USE

DHPCs with significant long-term changes in use							
INN (ATC)	Approval date	DHPC date	Safety issue (SOC)	Median (No. of Rx 12 month pre-DHPC)	Standardized effect size	*p*- value	No. of observations (used for analysis)
cisapride (A03FA02)	Jul-88	Sep-02	Electrocardiogram QT prolonged (Investigations)	4,148.5	-0.433	0.000	108
rosiglitazone (A10BG02)	Jul-00	Jan-06	Macular edema (Eye)	1,488	-0.327	0.000	108
rosiglitazone (A10BG02)	Jul-00	Mar-07	Fracture (Musculoskeletal)	964	-0.637	0.000	108
pioglitazone (A10BG03)	Oct-00	Apr-07	Fracture (Musculoskeletal)	1,012	-0.320	0.005	84
desogestrel and ethinylestradiol (G03AA09)	May-81	Sep-01	Venous thrombosis (Vascular)	10,605	-0.153	0.001	108
gestodene and ethinylestradiol (G03AA10)	May-89	Sep-01	Venous thrombosis (Vascular)	5,719.5	-0.208	0.000	108
itraconazole (J02AC02)	Oct-90	May-01	Cardiac failure (Cardiac)	8,834.5	-0.097	0.006	108
lopinavir/ritonavir (J05AE06)	Mar-01	Sep-06	Circumstance or information capable of leading to medication error (Injury)	94.5	0.154	0.011	89
didanosine (J05AF02)	Aug-00	Mar-05	Drug effect decreased (General)	40.5	-0.438	0.002	108
leflunomide (L04AA13)	Sep-99	Mar-01	Hepatitis (Hepatobiliary)	432	-0.315	0.000	108
piroxicam (M01AC01)	Jun-87	Aug-07	Gastrointestinal disorder (Gastrointestinal)	2,920.5	-0.494	0.000	108
celecoxib (M01AH01)	May-00	Dec-04	Cardiovascular disorder (Cardiac)	11,851.5	-0.570	0.000	72
etoricoxib (M01AH05)	Jul-02	Feb-05	Cardiovascular disorder (Cardiac)	12,375.5	-0.153	0.006	68
strontium ranelate (M05BX03)	Sep-04	Nov-07	Drug rash with eosinophilia and systemic symptoms: DRESS (Blood)	344.5	-0.674	0.000	41
vigabatrine (N03AG04)	Sep-90	Sep-02	Visual field defect (Nervous)	40	-0.186	0.007	108
lamotrigine (N03AX09)	Jan-96	Jun-06	Maternal drugs affecting fetus (Injury)	746	-0.155	0.001	108

Appendix 3.1: Characteristics of DHPCs with and without long-term impact on drug use *(continued)*

DHPCs with significant long-term changes in use							
INN (ATC)	**Approval date**	**DHPC date**	**Safety issue (SOC)**	**Median (No. of Rx 12 month pre-DHPC)**	**Standardized effect size**	***p*- value**	**No. of observations (used for analysis)**
pergolide (N04BC02)	Jul-91	Apr-05	Cardiac valve disease (Cardiac)	142	-0.245	0.008	108
olanzapine (N05AH03)	Sep-96	Mar-04	Death (General)	2,193	-0.171	0.009	70
paroxetine (N06AB05)	Jun-91	Mar-06	Maternal drugs affecting fetus (Injury)	10,613	-0.145	0.044	67
bupropion (N06AX12)	Dec-99	May-01	Convulsion (Nervous)	4,399.5	-0.406	0.000	108
DHPCs without significant long-term changes in use							
cisapride (A03FA02)	Jul-88	Sep-04	Electrocardiogram QT prolonged (Investigations)	408.5	0.155	0.880	108
sibutramine (A08AA10)	Apr-01	Jul-02	Cardiovascular disorder (Cardiac)	567.5	0.001	0.998	92
repaglinide (A10BX02)	Aug-98	May-03	Hypoglycaemia (Endocrine)	47.5	-0.193	0.283	108
epoetin alfa (B03XA01)	Nov-88	Nov-01	Aplasia pure red cell (Blood)	417	0.078	0.563	108
epoetin alfa (B03XA01)	Nov-88	Jul-02	Aplasia pure red cell (Blood)	495.5	0.201	0.076	108
epoetin alfa (B03XA01)	Nov-88	Dec-02	Aplasia pure red cell (Blood)	551.5	-0.114	0.256	108
rosuvastatin (C10AA07)	Nov-02	Jun-04	Rhabdomyolysis (Musculoskeletal)	5,968.5	0.122	0.312	70
gemfibrozil (C10AB04)	Jul-90	May-03	Hypoglycaemia (Endocrine)	595	0.029	0.747	108
tacrolimus (D11AX14)	Apr-96	Apr-06	Lymphoma (Blood)	1,550.5	-0.199	0.147	108
pimecrolimus (D11AX15)	Apr-03	Apr-06	Lymphoma (Blood)	913.5	-0.074	0.513	67
hormone supplementation therapy (G03F)	Jul-76	Dec-03	Breast cancer (Neoplasms)	2,951	0.104	0.375	108
tamsulosine (G04CA02)	Apr-95	Aug-06	Floppy iris syndrome (Nervous)	6,142	0.016	0.749	108

Appendix 3.1: Characteristics of DHPCs with and without long-term impact on drug use *(continued)*

DHPCs without significant long-term changes in use							
INN (ATC)	**Approval date**	**DHPC date**	**Safety issue (SOC)**	**Median (No. of Rx 12 month pre-DHPC)**	**Standardized effect size**	***p*- value**	**No. of observations (used for analysis)**
somatropin (H01AC01)	Nov-91	Jun-07	Circumstance or information capable of leading to medication error (Injury)	116.5	-0.144	0.180	108
triamcinolon acetonide (H02AB08)	Sep-66	Dec-06	Eye disorder (Eye)	11,643.5	-0.091	0.225	108
nelfinavir (J05AE04)	Jan-98	Jun-07 & Jul-07*	Therapeutic product contamination (Injury)	15	-0.139	0.561	108
lopinavir/ritonavir (J05AE06)	Mar-01	Aug-07	Incorrect dose administered (Injury)	109.5	0.036	0.476	89
stavudine (J05AF04)	May-96	Sep-01	Muscular weakness (Nervous)	73.5	-0.045	0.580	108
tenofovir (J05AF07)	Feb-02	Jul-03	Drug effect decreased (General)	97.5	0.206	0.324	74
tenofovir (J05AF07)	Feb-02	Oct-03	Drug effect decreased (General)	97.5	-0.284	0.176	74
tenofovir (J05AF07)	Feb-02	Mar-05	Drug effect decreased (General)	137	-0.010	0.947	74
tenofovir (J05AF07)	Feb-02	Mar-06	Renal disorder (Renal)	167.5	0.163	0.183	74
nevirapine (J05AG01)	Feb-98	Feb-04	Skin reaction (Skin)	86.5	0.035	0.679	108
imatinib mesilate (L01XE01)	Nov-01	Mar-05	Urinary bladder adenoma (Renal)	37.5	0.188	0.320	60
imatinib mesilate (L01XE01)	Nov-01	Dec-06	Cardiac failure (Cardiac)	53.5	-0.197	0.175	60
hydroxycarbamide (L01XX05)	Nov-72	Dec-05	Cutaneous vasculitis (Skin)	133	0.047	0.212	108
letrozol (L02BG04)	Jan-97	Dec-05	Maternal drugs affecting fetus (Injury)	240.5	0.139	0.089	108
mycophenolate mofetil (L04AA06)	Feb-96	Nov-07	Maternal drugs affecting fetus (Injury)	274	-0.028	0.602	108
sirolimus (L04AA10)	Mar-01	Feb-03	Bronchial anastomosis complication (Respiratory)	6.5	0.717	0.084	94

Appendix 3.1: Characteristics of DHPCs with and without long-term impact on drug use *(continued)*

DHPCs without significant long-term changes in use							
INN (ATC)	**Approval date**	**DHPC date**	**Safety issue (SOC)**	**Median (No. of Rx 12 month pre-DHPC)**	**Standardized effect size**	***p*- value**	**No. of observations (used for analysis)**
etanercept (L04AB01)	Feb-00	Feb-03	Infection (Infections)	28	-0.041	0.961	108
celecoxib (M01AH01)	May-00	Feb-05	Cardiovascular disorder (Cardiac)	11,851.5	0.037	0.582	72
botulin a toxin (M03AX01)	Dec-93	Jun-07	Muscular weakness (Nervous)	25	-0.030	0.883	108
lamotrigine (N03AX09)	Jan-96	Oct-05	Drug effect decreased (General)	688	0.075	0.152	108
topiramate (N03AX11)	Jun-99	Oct-01	Oculomucocutaneous syndrome (Eye)	142	-0.048	0.868	108
levetiracetam (N03AX14)	Sep-00	Nov-07	Incorrect dose administered (Injury)	701	0.055	0.087	86
paroxetine (N06AB05)	Jun-91	Jan-06	Maternal drugs affecting fetus (Injury)	10,451	0.041	0.658	108
venlafaxine (N06AX16)	Dec-97	Sep-03	Suicidal ideation (Psychiatric)	4,222.5	0.105	0.128	108
galantamine (N06DA04)	Jul-03	Oct-05	Death (General)	232	-0.075	0.559	61
salbutamol (R03AC02)	Dec-73	May-07	Myocardial ischaemia (Cardiac)	53,595.5	-0.114	0.105	108

* The two DHPCs issued for nelfinavir were issued close in time and were therefore treated as a single intervention and analyzed together. The first DHPC was taken as the time point of intervention. **Legend**: **INN**: International Proprietary Name; **ATC**: Anatomical Therapeutic Chemical; **DHPC**: Direct Healthcare Professional Communication; **SOC**: System Organ Class; **Rx**: Medical prescription.

System Organ Class according to MedRA:

Investigations: Investigations; Eye: Eye disorders; Musculoskeletal: Muscolo-skeletal and connective tissue disorders; Vascular: Vascular disorders; Cardiac: Cardiac disorders; Injury: Injury, poisoning and procedural complications; General: General disorders and administration site conditions; Hepatobiliary: Hepatobiliary disorders; Gastrointestinal: Gastrointestinal disorders; Blood: Blood and lymphatic system disorders; Nervous: Nervous system disorders; Endocrine: Endocrine disorders; Neoplasms: Neoplasms benign, malignant and unspecified (incl cysts and polyps); Renal: Renal and urinary disorders; Skin: Skin and subcutaneous tissue disorders; Respiratory: Respiratory, thoracic and mediastinal disorders; Infections: Infections and infestations; Psychiatric: Psychiatric disorders.

APPENDIX 3.2: BOX-JENKINS ARIMA MODELS AND INTERRUPTED TIME SERIES ANALYSIS

In this appendix we give a schematic overview of the analytical procedure we used for the time series intervention models.

Intervention analysis or interrupted time series analysis (ITS) is used to evaluate the impact of a discrete intervention (here: a regulatory action in the form of a DHPC) on a time series. The standard time series approach to intervention analysis is based on Box-Jenkins ARIMA models (Box and Tiao 1975; McDowall et al. 1980).[13] We closely follow the procedures outlined in McDowall et al. (1980) and keep the discussion at a more general level. We first present the ARIMA model and the Box-Jenkins approach which serve as basic framework for the ITS. Thereafter, we describe the intervention model.

ARIMA models and Box-Jenkins Approach

*A*uto*R*egressive (*I*ntegrated) *M*oving *A*verage (AR(I)MA) models are the most general univariate time series models. The general ARIMA model has three structural parameters p, q, and d, and is commonly expressed as ARIMA (p,d,q). The parameters p and q are the orders of the autoregressive (AR) and moving average (MA) part, respectively.
An AR process of order p can be denoted as

$$\varphi_p(B)y_t = \mu + \varepsilon_t, \quad t=1,....,T, \tag{3.1}$$
$$\text{with } \varphi_p(B) = (1 - \varphi_1 B - \varphi_2 B^2 - ... - \varphi_p B^p).$$

The q-order MA process is

$$y_t = \mu + \theta_q(B)\varepsilon_t, \quad t=1,....,T, \tag{3.2}$$
$$\text{with } \theta_q(B) = (1 - \theta_1 B - \theta_2 B^2 - ... - \theta_q B^q).$$

B is the backshift operator, defined by $B^k y_t = y_{t-k}$.
The parameter d indicates the order of differencing. The differencing operator is given by $\Delta^d = (1-B)^d$.

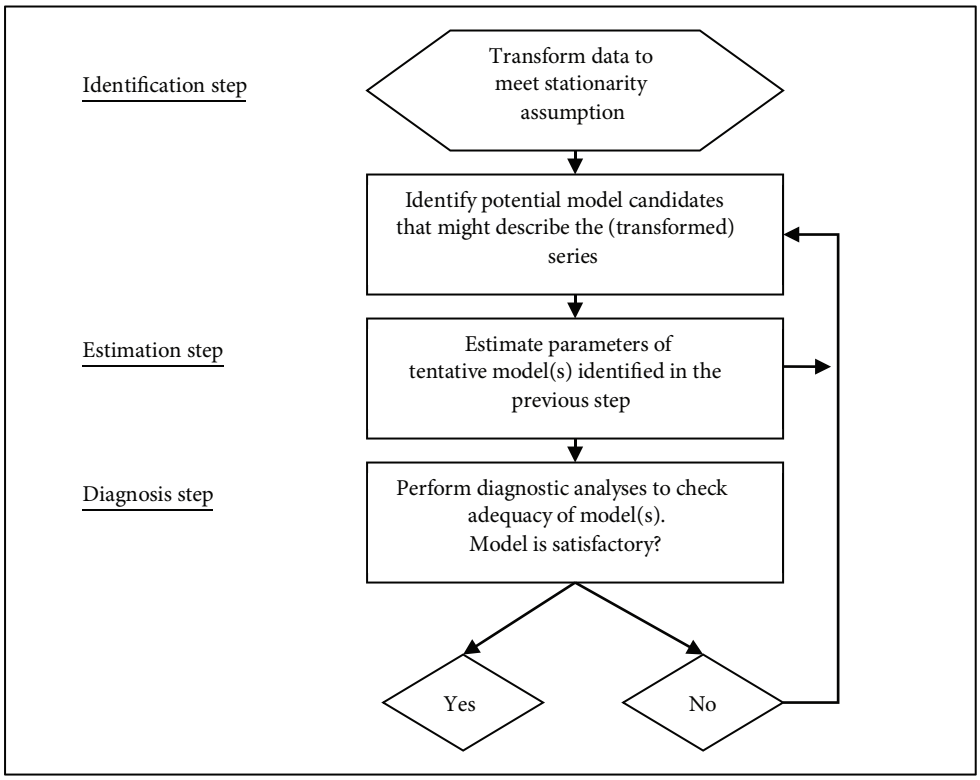
The ARIMA model can then be expressed as

$$\varphi_p(B)\Delta^d y_t = \mu + \theta_q(B)\varepsilon_t, \quad t=1,....,T. \tag{3.3}$$

[13] Because a detailed description of the 46 time series models that we estimated would go beyond the scope of this chapter we limit ourselves to a general discussion.

The approach proposed by Box and Jenkins involves three basic steps which are shown in Figure 1.

Figure 1: Model-building strategy



adapted from McDowall et al. 1980 (p.47ff)

At first, if necessary, a suitable transformation of the data needs to be selected to achieve stationarity. There are different forms of stationarity. In the present context, the more common concept of covariance stationarity is considered. Covariance stationarity implies that the properties of the underlying model do not depend on time. To put it more formally, a series y_t is said to be covariance stationary if its mean, its variance, and its (auto)covariance are finite-valued numbers and constant through time.

In practice, visual inspection of the estimated autocorrelation (ACF) and partial autocorrelation function (PACF), as well as statistical tests (so-called unit root tests) are used to examine whether the data series behaves in a (non)stationary way. Several types of tests

exist, a prominent example being the Augmented Dickey-Fuller (ADF) unit root test for non-stationarity.[14] The ACF and PACF also give initial information about an autoregressive and/or moving average structure and the respective order.

After tentative model candidates have been identified, the AR and MA parameters φ and θ can be estimated. The parameters must satisfy the stationary/invertibility condition and need to be statistically significant. For an AR(1) process the first criterion of stationarity is fulfilled if the absolute value of φ is less than 1. Similar, an MA(1) process requires an absolute value of θ smaller than 1 to satisfy the condition of invertibility.[15]

Finally, statistical adequacy and validity of the model are assessed to ensure that the fitted model is consistent with the properties of the data and reasonably parsimonious. Various checks may be performed on the residuals estimated in the previous step to examine whether they form a random series, a prerequisite for model adequacy. Generally, diagnostic checks involve both the inspection of the estimated residual ACF and statistical tests. Residual plots can serve as a first means to detect whether there are departures from randomness. A commonly used test statistic is the Ljung-Box-Q-Statistic which considers the residual autocorrelations as a whole rather than individually. Other standard statistical test employed to check the presence of serial correlation are the Durbin-Watson test for first-order autocorrelation and the more general Beusch-Godfrey LM test for higher-order serial dependence. If there is more than one model that meets the requirements of the different steps, information criteria such as the Akaike (AIC) or Schwarz Information Criterion (SIC) assist in selecting the final model.

The procedure is iterative in a sense that if, at any step, the model is deemed to violate the requirements the steps are repeated until a satisfactory model formulation is found.

Intervention analysis (ITS)

Once adequate ARIMA models have been developed for each series the intervention component is introduced to model the impact of the regulatory actions. In the present case the time point of the intervention is known.

Suppose y_{t-1}, y_t, y_{t+1}, are observations obtained at equal time intervals. The general form of an intervention model may be written as (Box and Tiao 1975; McDowall et al. 1980):

$$y_t = f(I_t) + N_t \tag{3.4}$$

14 Details and a testing framework can be found in Enders 2010, Chapter 4.

15 For AR(2) and MA(2) processes the stationary /invertibility requirements involve three conditions; $|\varphi_2| < 1$; $\varphi_2 + \varphi_1 < 1$; $\varphi_2 - \varphi_1 < 1$ for stationarity and $|\theta_2| < 1$; $\theta_2 + \theta_1 < 1$; $\theta_2 - \theta_1 < 1$ for invertibility, respectively. Since higher-order processes are rarely observed in practice we do not consider them here.

where $N_t$is a stochastic process representing the observed time series, the 'noise' part which is assumed to follow an AR(I)MA process as described above; and where $f(I_t)$ represents the intervention component of the model (deterministic part) and is the response of the system to a dummy variable I_t.

I_t can take the following functional forms:

a) A pulse function

$$I_t = \begin{cases} 1 & \text{for } t = T \\ 0 & \text{else} \end{cases} \tag{3.5}$$

b) A step function

$$I_t = \begin{cases} 1 & \text{for } t \geq T \\ 0 & \text{prior to the intervention} \end{cases} \tag{3.6}$$

The pulse function represents an intervention whose impact lasts for one moment. The change is thus only temporary. The step intervention allows the impact of the event to remain throughout the time frame under study. In the present study the intervention is modeled as a step function, where the level change is assumed to be permanent after the intervention.

Response to an intervention

Assuming that a system change following an intervention is noticed b periods after the intervention the response can be modeled as $\omega B^b I_t$, where B^b is a backshift operator that lags a variable by b periods and I_t is a step function. The parameter ω measures the 'magnitude' of the impact. In the case of an instantaneous, permanent impact the intervention component is $f(I_t) = \omega_0 I_t$. A more general representation of a response is given by the function,

$$\frac{\omega(B)}{\alpha(B)} I_t, \tag{3.7}$$

with $\omega(B) = \omega_0 B + \omega_1 B + \omega_2 B^2 + ... + \omega_m B^m$ and $\alpha(B) = \alpha_0 B + \alpha_1 B + \alpha_2 B^2 + ... + \alpha_n B^n$, where $\alpha(B)$ is the gradual adjustment of y to the intervention over time. We refer to Box and Tiao (1975) for an extended discussion.

Chapter 4

Direct Healthcare Professional Communications: when do they have an impact?*

A retrospective analysis of Direct Healthcare Professional Communication

4.1 INTRODUCTION

Due to the well-known limitations of pre-approval clinical trials, the safety profile of a drug is only partly known at the time of market entry (Stricker and Psaty 2004). Market approval does not signal the end of drug development, but the start of continuous evaluation of both benefits and risks during the entire lifecycle of a drug. Throughout this lifecycle serious safety issues may emerge (Giezen et al. 2008; Lasser et al, 2002; Mol et al. 2010), which can cause hospitalization, disability, or even death of patients (Pirmohamed et al. 2004; Sari et al. 2007). Healthcare professionals need to be informed of these safety issues as soon as possible in order to minimize the risk of preventable adverse drug events (ADEs). In the European Union, these risks are communicated through paper-based warning letters, so-called Direct Healthcare Professional Communications (DHPCs) or 'Dear Doctor Letters'. Over the last decade, risk minimization interventions such as DHPCs have been issued in increasing numbers to ensure continued safe and effective use of medicinal products (Mol et al. 2010; Nkeng et al. 2012).

However, the limited evidence indicates that DHPCs are not always effective in changing behavior of physicians (Dusetzina et al. 2012; Piening et al. 2012a). Most studies that have assessed the impact of drug safety warnings focus on one drug or on a limited number

* This chapter is based on Reber, K.C., Piening, S., Wieringa, J.E., Straus, S.M.J.M., Raine, J.M., de Graeff, P.A, Haaijer-Ruskamp, F.M., and Mol, P.G.M. (2012). When Direct Healthcare Professional Communications have an impact on inappropriate and unsafe use of medicines. *Clinical Pharmacology & Therapeutics*, forthcoming.

of warnings only, and often have methodological limitations (Piening et al. 2012a). When looking at a large number of different drug safety issues, we show that DHPCs lowered drug use in half of the cases in the short-term, and in a third of the cases in the long-term (Piening et al. 2012b).

With the new EU pharmacovigilance legislation which came into force in July 2012, evaluation of the impact of risk minimization measures has become mandatory (Directive 2010/84/EU; Regulation (EU) No. 1235/2010). Currently, it is unknown which determinants might influence the impact of DHPCs. A better understanding of the influence of these determinants can facilitate optimization of future risk communication and evaluation of risk minimization measures.

In this study we explore the impact of drug and DHPC related characteristics on the effect of DHPCs on drug use.

4.2 METHODS

4.2.1 Data collection

Data were collected for all drugs for which a DHPC was issued in the Netherlands between January 2001 and January 2008. Monthly dispensing data for the period 2000-2008 were obtained from the Dutch Foundation for Pharmaceutical Statistics. The DHPCs were collected from the website of the Dutch Medicines Evaluation Board (MEB) and the Dutch Healthcare Inspectorate paper archive. We excluded DHPCs for drugs that were not dispensed in ambulatory care, drugs with insufficient dispensing data (≤ 10 Rx/month for new users, who were not prescribed the same drug within the previous six month; pre- and post-DHPC), and drugs for which a market withdrawal was announced in the DHPC.

The drug and DHPC characteristics were retrieved from the DHPCs, the human medicines database of the MEB, the World Health Organization ATC classification system, and the Medical Dictionary for Regulatory Activities (MedDRA®, version 13)[16]. We recorded the International Nonproprietary Names (INN), Anatomical Therapeutic Chemical (ATC) classification, registration date, date of DHPC, and safety issue (including System Organ Class).

[16] The MedDRA terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations.

4.2.2 Data measurement

4.2.2.1 Outcome measure

The outcome measure for this study is the relative change in new drug use after a DHPC was issued. We define new drug use as the number of new prescriptions of a drug for which no prescriptions were dispensed to the patient in the previous six months. We chose new drug use as our outcome measure since we assume it to be more sensitive to changes in prescribing than overall drug use. The relative change was calculated as the absolute change in drug use divided by the median drug use in the 12 months before the DHPC. Changes in the absolute number of new drug use were determined through interrupted time series analyses based on separate autoregressive integrated moving average (ARIMA) models for each individual drug. Observed changes indicate a change in the level of new use from the time of the DHPC until the end of the observation period. The calculation of the outcome measure and in- and exclusion criteria are described in more detail elsewhere (Chapter 3; Piening et al. 2012b).

4.2.2.2 Determinants

Characteristics of the drugs and the DHPC were assessed to explain differences in the outcome. We included four drug related characteristics: (1) The *time to DHPC*, defined as the elapsed time in months from drug approval (registration date) to the publication of the DHPC. (2) *Trends in use before the DHPC*, based on trend analyses to identify changes in the number of new users in the 12 months before the publication of the DHPC (Piening et al. 2012b). (3) The *degree of therapeutic innovation* is determined by using the score of therapeutic innovation as reported by Motola et al. (2005) for drugs that were centrally approved in Europe. Using this score, drugs can be classified as important, moderate, modest, or as solely pharmacological/technological innovations, taking into account the seriousness of the disease, the availability of alternative drugs, and whether drug effects have been shown on relevant clinical endpoints and observed effect size. For the drugs that were approved via the decentralized system, that is at the national level, two investigators (PM and PdG) independently evaluated the degree of therapeutic innovation using the 'Motola algorithm'. In case of disagreement consensus was reached by discussion. (4) *Specialist drugs*, i.e., the drug required an initial prescription from a medical specialist as indicated in the Summary of Product Characteristics (SmPC).

The following three DHPC related characteristics were included: (1) *First or repeated DHPC*, a dichotomous variable indicating whether the DHPC was the first safety-related regulatory action or whether another DHPC had been sent previously. This included identical as well as different safety issues. (2) *DHPC template*, a dichotomous variable indicating whether the DHPC was issued after a DHPC template had been published in Volume 9A of

'The rules governing medicinal products in the European Union' in January 2007. (3) The *type of serious safety issue*, which is classified according to the World Health Organization listing of serious adverse events or reactions, as resulting into: death, (prolongation of) hospitalization, and persistent or significant disability/incapacity (WHO 2011). We added a category 'other' for cases that could not be classified into any of the aforementioned categories (e.g., product contamination). Two pharmacovigilance experts (medical doctors) independently categorized the adverse drug reactions. Any disagreement was resolved by a third expert (PM).

4.2.3 Statistical analysis

We performed a multiple linear regression analysis to examine the impact of drug and DHPC characteristics on the observed relative change in new drug use following a DHPC. As the assumption of homoscedasticity, one of the key assumptions in linear regression, was not fulfilled, a weighted least squares procedure was applied (Greene 2008). The size of the weight is inversely related to the uncertainty of the information contained in the associated data point. The point estimates of relative changes in new drug use weigh less when the observed absolute changes in effect sizes are found to have higher standard errors in the ARIMA model. The independent variables are entered blockwise, with the variables describing the drug characteristics entering in the first block. The second block includes the DHPC characteristics. The degree of therapeutic innovation is treated as a continuous, independent variable in the analysis. The explained variance of the model is indicated by the adjusted R^2. The significance of each block is tested using F change, and the contribution of each block to the variance explained is computed (ΔR^2). Raw coefficients (B) with 95% confidence intervals (CIs), standardized beta coefficients (β), and p-values are calculated.

4.3 RESULTS

We identify 59 DHPCs for 46 drugs that fulfill all in- and exclusion criteria. Two DHPCs that were issued within two consecutive months for nelfinavir are analyzed as one. This results in 58 evaluable drug and DHPC pairs for which the relative changes in new drug use following the DHPC are calculated (Table 4.1). The median number of new drug users per month in the year before the DHPC ranged from 7 (sirolimus) to 53,596 (salbutamol) (Appendix 4.1). The mean relative change in new drug use among all DHPCs analyzed is -9% (SD: 0.24) and ranges from -67.4% for strontium ranelate to +71.7% for sirolimus. The median time from approval to DHPC is 82.5 months (6.9 years, IQR: 3.4 – 13.6) and 80% of the DHPCs

Table 4.1: Descriptive statistics for outcome and independent variables

Variable	Drug & DHPC pair[a]
Sample	58
Outcome measure (Relative change in new drug use)	
Mean (SD)	-0.09 (0.24)
Range	-0.674 to 0.717
Independent variables	
Drug characteristics:	
Time to DHPC since registration	
Median, year (IQR)	6.9 (3.4 - 13.6)
≤ 3, year (%)	12 (20.7)
>3-10, year (%)	23 (39.7)
>10, year (%)	23 (39.7)
Trends in use (before DHPC was issued), No. (%)	
increasing use	16 (27.6)
no change in use	29 (50,0)
decreasing use	13 (22.4)
Degree of therapeutic innovation, No. (%)	
important	23 (39.7)
moderate	12 (20.7)
modest	4 (6.9)
solely pharmacological/technological	19 (32.8)
Specialist drug, No. (%)	
no	24 (41.4)
yes	34 (58.6)
DHPC characteristics:	
First/repeated DHPC, No. (%)	
first	41 (70.7)
repeated	17 (29.3)
DHPC template, No. (%)	
no	47 (81.0)
yes	11 (19.0)
Type of serious safety issue, No. (%)	
death	10 (17.2)
(prolonged) hospital admission	17 (29.3)
(temporary/persistent) disability or incapacity/teratogenicity	18 (31.0)
other	13 (22.4)

[a] Unless otherwise indicated, data are expressed as numbers (percentages) of drug & DHPC pairs. Percentages might not add up to 100% due to rounding. SD= standard deviation, IQR=interquartile range, y=years.

Table 4.2: Results of the weighted regression analysis[a]

	Blocks entered in the analysis	Model 1 (block 1 entered)			Model 2 (both blocks entered)		
		B [95% CI]	β	P value	B [95% CI]	β	P value
	(constant)	-0.214 [-0.386; -0.042]		0.016	-0.043 [-0.212; 0.126]		0.608
	Time to DHPC (months)	$3.05*10^{-4}$ [-0.000; 0.001]	0.149	0.257	$1.67*10^{-4}$ [-0.000; 0.001]	0.082	0.478
Block 1: drug	Trend in use (before DHPC)						
	increasing	ref	ref		ref	ref	
	no change	0.036 [-0.097; 0.169]	0.084	0.593	0.011 [-0.106; 0.128]	0.025	0.854
	decreasing	-0.080 [-0.242; 0.082]	-0.160	0.324	-0.135 [-0.273; -0.003]	-0.270	0.055
	Degree of therapeutic innovation[b]	-0.002 [-0.057; 0.052]	-0.013	0.934	0.004 [-0.044; 0.053]	0.025	0.860
	Specialist drug						
	No	ref	ref		ref	ref	
	Yes	**0.136 [0.002; 0.269]**	**0.320**	**0.046**	**0.159 [0.043; 0.274]**	**0.373**	**0.008**
Block 2: DHPC	First/repeated DHPC						
	First				ref	ref	
	Repeated				-0.092 [-0.213; 0.029]	-0.187	0.133
	DHPC template						
	No				ref	ref	
	Yes				**-0.157 [-0.266; -0.049]**	**-0.308**	**0.005**
	Type of serious safety issue						
	Death				**-0.265 [-0.415; -0.114]**	**-0.450**	**0.001**
	Hospital admission				-0.012 [-0.152; 0.129]	-0.025	0.867
	Disability/Incapacity/Teratogenicity				**-0.155 [-0.288; -0.023]**	**-0.348**	**0.023**
	Other				ref	ref	
	R^2 (adjusted R^2)		0.184 (0.106)			0.499 (0.392)	
	ΔR^2					0.315	
	F change					5.906	0.000

[a] A negative regression coefficient is associated with a lower use post DHPC (i.e., a larger decrease or a smaller increase as a result of the DHPC). [b] Treated as continuous predictor. **Legend:** B= raw regression coefficient; 95% CI= 95% confidence interval; β= standardized regression coefficient; ref= reference category.

are issued for drugs that have been licensed for more than three years. Almost a quarter of the drugs show a decrease in new drug use prior to the DHPC. Similar numbers of DHPCs are issued for all drugs independent of their degree of innovation (important, moderate and solely pharmacological/technological) with a few drugs classified as modestly innovative. More than half (59%) of the DHPCs are sent for specialist drugs. The majority (71%) of the 58 DHPCs concerns a first DHPC. DHPCs are evenly divided over the seriousness categories.

When the first block with the drug characteristics was entered in the model to test if these characteristics explained any differences in the impact of the DHPC on drug use, we found that DHPCs sent for specialist drugs were associated with a more positive change in use than the change in use of non-specialist drugs (Table 4.2; Model 1, p= .046). Within the group of drugs for which the DHPC led to a decrease in use, the positive β value indicated that the negative usage effect was (partially) offset for specialist drugs. Conversely, for the cases where a DHPC increased drug use, the increase was stronger for specialist drugs than for non-specialist drugs. This effect remains significant after entering the DHPC characteristics in the model (Table 4.2; Model 2, p= .008). In the second model, we also find that DHPCs for drugs with a decreasing pre-DHPC trend are associated with a change towards lower drug use; this effect is marginally significant (Table 4.2; Model 2, p=.055). DHPCs issued after a template was made available contribute to a change towards lower drug use (Table 4.2; Model 2, p<.05). Both safety issues with a risk of death as well as disability are significantly associated with changes towards lower drug use (Table 4.2; Model 2, p<.05 for both), whereas no significant impact is observed for safety issues regarding the risk of hospitalization (Table 4.2; Model 2, p=.867).

The block of DHPC characteristics contributes significantly to the model, explaining an additional 32% of variance (F-change=5.906, ΔR^2=0.315, p<.001). The drug and DHPC characteristics together explain 39% (adj. R^2=0.392) of the overall variation in change of new drug use.

4.4 COMMENT

This study gives a first impression of the determinants that increase the impact of DHPCs on drug use. We find that declining drug use prior to the DHPC, specialist drugs, the type of serious safety issue, and the availability of a DHPC template are associated with changes in drug use. We discuss the comments from the viewpoint of the most common situation that a DHPC leads to a decrease in the number of new users.

The marginally significant effect found for already declining use pre-DHPC confirms our earlier assumption that DHPCs have an accelerating effect on the decline in use of drugs that are at the end of their lifecycle, when several substitute drugs have become available (Piening et al. 2012b).

As hypothesized earlier (Piening et al. 2012b), we observe that DHPCs issued for drugs that require a specialist to initiate prescribing have less impact compared to those sent for drugs that can also be prescribed by a GP. Drugs are given this requirement in the SmPC, because of the expected complexity in prescribing them. The specialist drugs in our sample are mainly prescribed for the human immunodeficiency virus (HIV), epilepsy, and cancer. Specialists often have additional resources at their disposition to monitor their patients, which facilitates continued use of a drug post-DHPC (Harrold et al. 1999). Another explanation could be that the perception of their own expertise limits their willingness to accept recommendations from others, as was observed during implementation of treatment guidelines (Kasje et al. 2002). Also, specialists might need to continue these more risky treatment options since they treat more complex patients that previously failed on other therapies.

Towards the end of our study period the European guidelines were amended to include a fixed DHPC template (EC 2008). When we analyze the content of the DHPCs in our sample, we observe an increase in uniformity of the structure and layout of the DHPCs. The results of our analysis confirm that DHPCs issued after the DHPC template was made available have more impact compared to DHPCs issued before the availability of the template. This suggests that the DHPC template has contributed to the understandability and uptake of the safety information, which would be in line with earlier findings that explicit wording contributes to improved uptake of DHPC recommendations (Weatherby et al. 2002).

Communicating on serious safety issues potentially causing death or disability leads to significantly lower drug use. Even though all DHPCs are issued for serious safety issues, it is to be expected that these particularly serious safety issues will affect prescribing behavior of physicians more (Piening et al. 2012b).

The impact of DHPCs is not influenced by the age of the drug, suggesting that DHPCs affect the use of older and younger drugs in the same way. This is consistent with an earlier finding that important safety issues requiring DHPCs are identified throughout the entire lifecycle of drugs (Mol et al. 2010), which would indicate that the age of the drug does not need to be considered when tailoring the communicating drug safety issues.

More innovative drugs do not show greater impact of a DHPC on drug use than less innovative drugs. Therapeutically innovative drugs can provide physicians with treatment

options for complex patients who do not respond well to less innovative drugs. Physicians could be of the opinion that the innovativeness of the drug outweighs the risk of occurrence of the safety issue. However, our level of analysis does not allow us to elaborate how this translates to behavior of individual physicians. This aspect could be explored in a focus group setting or by conducting individual interviews with prescribers.

Our results show that a repeated safety warning is not necessarily more effective in changing drug use than a single DHPC. This is consistent with findings of several prior studies that report no changes in the assessed outcome after repeated safety warnings were issued (Jones, J.K. et al. 2001; Kurdyak et al. 2007; Kurian et al. 2007; Olfson et al. 2008). The repeated DHPCs in our sample concern both identical as well as different safety issues. Possibly, repeated DHPCs issued for the same safety issue are more effective than repeated DHPCs issued for different safety issues with the same drug. However, due to the limited sample size, we are not able to incorporate this aspect into our model.

4.4.1 Strengths and limitations

To our knowledge, this study is the first to systematically evaluate determinants of the impact of DHPCs on new drug use. We include a large number of DHPCs in our analyses, covering a wide variety of drugs and safety issues. With the results of this study it will be possible to anticipate and possibly enhance the impact of future DHPCs on drug use by tailoring risk communication about safety issues of drugs more specifically. In certain cases, it can be anticipated that an additional communication method needs to be deployed when a reduction in use is the desired outcome. For example, in case of a DHPC that is issued for a safety issue with a risk of hospitalization, the professional associations could be involved in the communication process. They could also inform their members, either by e-mail or in their news bulletins.

We include a set of seven factors in our full model, however, the range of determinants is limited due to the sample size and its corresponding power. Our full model explains 39% of the overall variation in DHPC effect size and can be considered as a first exploration of determinants that influence the impact of DHPCs. Other factors that we could not account for in our model might also attribute to variations in the impact of DHPCs, for example media attention, the incidence of safety issues, safety issues related to off-label use, and availability of an alternative treatment. It is suggested that media attention can play an important role in influencing the impact of DHPCs (Martin et al. 2006). In particular, extensive media attention for certain drug safety issues (e.g. rofecoxib, rosiglitazone) may have contributed to increased awareness of prescribers regarding drug safety warnings (Raine et al. 2011). To probe this, we

performed an explorative lay- and professional literature search for a selection of the DHPCs in our study population. This search resulted in too little information to include presence of media attention in our model. Likewise, the incidence of the safety issue cannot be included, since this aspect was not mentioned in the majority of the DHPCs. Too few DHPCs concerned safety issues related to off-label use, leading to insufficient variation within the variable for incorporation into our model. Alternative treatment is available for almost all drugs and is indirectly covered in the innovation variable. We do not find associations for older versus newer drugs and degree of innovation with DHPC impact. Therefore, it seems unlikely that availability of an alternative treatment is a major determinant. The limited sample size could be addressed by repeating this study in a few years, when more DHPCs will be issued.

In addition, our study is limited to the Dutch setting. Also, extrapolation of these findings to hospital drugs is not possible. An EU wide study would allow for comparison of the impact of DHPCs as well as the determinants of impact of DHPCs in different countries. This will provide much needed information regarding locally tailored risk communicating strategies.

It should be noted that a decrease in use is not always the desired impact of a DHPC. The results of this study can thus only be used to anticipate the impact of DHPCs on new drug use, not for other outcomes that might be more attuned to the recommendation in the DHPC, such as necessity for liver function tests performed in case of risk of hepatotoxicity. This means that any additional action should be carefully considered. Nevertheless, we think that new drug use is the most appropriate outcome measure to explore the role of determinants of impact of DHPCs, because it is the single outcome measure that can reliably be assessed for such a large group of drugs. Also, new use is a more sensitive measure than overall use, since changes in prescribing behavior can more likely be expected in new users. Further research could be aimed at clusters of drugs with the same recommendation in the DHPC, e.g., all drugs which require laboratory testing, or all drugs with restrictions regarding concomitant use of contraindicated drugs. This may provide insight into how the impact of DHPCs on more specific outcomes can best be anticipated.

4.4.2 Conclusion and recommendation

This study provides a first exploration of determinants that influence the impact of DHPCs on drug use. The results show that declining use prior to the DHPC, specialist drugs, DHPCs issued after availability of a DHPC template, and the type of serious safety issue are associated with changes in new drug use. These results can be used as a first step in tailoring risk communication about safety issues of drugs more specifically.

APPENDIX 4.1: CHARACTERISTICS OF DRUGS AND DHPCS

DHPCs with significant long-term changes in use

Drug Characteristics				DHPC Characteristics				Drug use		DHPC impact	
INN (ATC)	Appr. date	Initial prescriber	Inno-vativeness	DHPC date	First/ Repeated DHPC	Safety issue (SOC)	Serious-ness	Median Rx before	Trend	Change in new drug use	
										Absolute (SE)	Relative
cisapride[1] (A03FA02)	Jul-88	S	4	Sep-02	repeat	Electrocardiogram QT prolonged (Investigations)	F	4148.5	↓	-1797.29 (420.10)	-0.433
rosiglitazone[1] (A10BG02)	Jul-00	GP	1	Jan-06	first	Macular oedema (Eye)	D	1488	0	-486.49 (79.35)	-0.327
rosiglitazone[2] (A10BG02)	Jul-00	GP	1	Mar-07	repeat	Fracture (Musculoskeletal)	D	964	↓	-614.12 (83.39)	-0.637
pioglitazone (A10BG03)	Oct-00	GP	1	Apr-07	first	Fracture (Musculoskeletal)	D	1012	0	-323.43 (110.85)	-0.320
desogestrel / ethinylestradiol (G03AA09)	May-81	GP	1	Sep-01	first	Venous thrombosis (Vascular)	H	10605	↓	-1618.97 (455.50)	-0.153
gestodene / ethinylestradiol (G03AA10)	May-89	GP	1	Sep-01	first	Venous thrombosis (Vascular)	H	5719.5	↓	-1187.13 (247.83)	-0.208
itraconazole (J02AC02)	Oct-90	GP	3	May-01	first	Cardiac failure (Cardiac)	O	8834.5	↓	-860.33 (305.63)	-0.097
lopinavir / ritonavir[1] (J05AE06)	Mar-01	S	4	Sep-06	first	Circumstance or information capable of leading to medication error (Injury)	O	94.5	0	14.55 (5.62)	0.154
didanosine (J05AF02)	Aug-00	S	4	Mar-05	repeat	Drug effect decreased (General)	H	40.5	↓	-17.72 (4.56)	-0.438

Appendix 4.1: Characteristics of drugs and DHPCs *(continued)*

DHPCs with significant long-term changes in use											
Drug Characteristics				DHPC Characteristics				Drug use		DHPC impact	
INN (ATC)	Appr. date	Initial prescriber	Inno-vativeness	DHPC date	First/ Repeated DHPC	Safety issue (SOC)	Serious-ness	Median Rx before	Trend	Change in new drug use	
										Absolute (SE)	Relative
leflunomide (L04AA13)	Sep-99	S	1	Mar-01	first	Hepatitis (Hepatobiliary)	F	432	↓	-135.92 (30.38)	-0.315
piroxicam (M01AC01)	Jun-87	GP	1	Aug-07	first	Gastrointestinal disorder (Gastrointestinal)	D	2920.5	↓	-1442.00 (214.23)	-0.494
celecoxib[1] (M01AH01)	May-00	GP	1	Dec-04	first	Cardiovascular disorder (Cardiac)	F	11851.5	↑	-6751.75 (1314.84)	-0.570
etoricoxib (M01AH05)	Jul-02	GP	1	Feb-05	first	Cardiovascular disorder (Cardiac)	H	12375.5	0	-1898.57 (666.33)	-0.153
strontium ranelate (M05BX03)	Sep-04	GP	3	Nov-07	first	Drug rash with eosinophilia and systemic symptoms: DRESS (Blood)	F	344.5	↑	-232.04 (15.6)	-0.674
vigabatrine (N03AG04)	Sep-90	S	3	Sep-02	repeat	Visual field defect (Nervous)	D	40	0	-7.43 (2.72)	-0.186
lamotrigine[2] (N03AX09)	Jan-96	S	3	Jun-06	repeat	Maternal drugs affecting fetus (Injury)	D	746	0	-115.28 (34.67)	-0.155
pergolide (N04BC02)	Jul-91	S	3	Apr-05	first	Cardiac valve disease (Cardiac)	D	142	0	-34.85 (10.04)	-0.245
olanzapine (N05AH03)	Sep-96	GP	3	Mar-04	first	Death (General)	F	2193	↑	-374.05 (140.18)	-0.171
paroxetine[2] (N06AB05)	Jun-91	GP	2	Mar-06	repeat	Maternal drugs affecting fetus (Injury)	D	10613	↑	-1534.58 (752.14)	-0.145
bupropion (N06AX12)	Dec-99	GP	3	May-01	first	Convulsion (Nervous)	D	4399.5	0	-1785.26 (440.44)	-0.406

Appendix 4.1: Characteristics of drugs and DHPCs *(continued)*

DHPCs without significant long-term changes in use											
Drug Characteristics				DHPC Characteristics			Drug use			DHPC impact	
INN (ATC)	Appr. date	Initial prescriber	Inno-vativeness	DHPC date	First/ Repeated DHPC	Safety issue (SOC)	Type of serious safety issue	Median Rx before	Trend	Change in new drug use	
										Absolute (SE)	Relative
cisapride[2] (A03FA02)	Jul-88	S	4	Sep-04	repeat	Electrocardiogram QT prolonged (Investigations)	O	408.5	↓	63.49 (419.54)	0.155
sibutramine (A08AA10)	Apr-01	GP	1	Jul-02	first	Cardiovascular disorder (Cardiac)	O	567.5	0	0.29 (100.02)	0.001
repaglinide (A10BX02)	Aug-98	GP	1	May-03	first	Hypoglycaemia (Endocrine)	H	47.5	0	-9.18 (8.51)	-0.193
epoetin alfa[1] (B03XA01)	Nov-88	S	4	Nov-01	first	Aplasia pure red cell (Blood)	H	417	↑	32.42 (55.88)	0.078
epoetin alfa[2] (B03XA01)	Nov-88	S	4	Jul-02	repeat	Aplasia pure red cell (Blood)	H	495.5	↑	99.64 (55.66)	0.201
epoetin alfa[3] (B03XA01)	Nov-88	S	4	Dec-02	repeat	Aplasia pure red cell (Blood)	H	551.5	↑	-62.85 (55.05)	-0.114
rosuvastatin (C10AA07)	Nov-02	GP	1	Jun-04	first	Rhabdomyolysis (Musculoskeletal)	H	5968.5	0	726.26 (711.06)	0.122
gemfibrozil (C10AB04)	Jul-90	GP	3	May-03	first	Hypoglycaemia (Endocrine)	H	595	↓	17.30 (53.41)	0.029
tacrolimus (D11AX14)	Apr-96	S	4	Apr-06	first	Lymphoma (Blood)	D	1550.5	0	-308.22 (210.02)	-0.199
pimecrolimus (D11AX15)	Apr-03	S	1	Apr-06	first	Lymphoma (Blood)	D	913.5	↓	-67.97 (103.45)	-0.074

Appendix 4.1: Characteristics of drugs and DHPCs *(continued)*

DHPCs without significant long-term changes in use											
Drug Characteristics				DHPC Characteristics				Drug use		DHPC impact	
INN (ATC)	Appr. date	Initial prescriber	Inno-vativeness	DHPC date	First/ Repeated DHPC	Safety issue (SOC)	Type of serious safety issue	Median Rx before	Trend	Change in new drug use	
										Absolute (SE)	Relative
hormone supplementation therapy (G03F)	Jul-76	GP	4	Dec-03	first	Breast cancer (Neoplasms)	H	2951	↓	307.82 (345.68)	0.104
tamsulosin (G04CA02)	Apr-95	GP	1	Aug-06	first	Floppy iris syndrome (Nervous)	D	6142	0	100.36 (313.28)	0.016
somatropin (H01AC01)	Nov-91	S	1	Jun-07	first	Circumstance or information capable of leading to medication error (Injury)	O	116.5	0	-16.81 (12.47)	-0.144
triamcinolon acetonide (H02AB08)	Sep-66	GP	2	Dec-06	first	Eye disorder (Eye)	O	11643.5	0	-1055.56 (863.04)	-0.091
nelfinavir[1, 2] (J05AE04)	Jan-98	S	4	Jun-07 & Jul-07*	first	Therapeutic product contamination (Injury)	O	15.5	0	-2.09 (3.58)	-0.139
lopinavir / ritonavir[2] (J05AE06)	Mar-01	S	4	Aug-07	repeat	Incorrect dose administered (Injury)	H	109.5	0	3.90 (5.44)	0.036
stavudine (J05AF04)	May-96	S	4	Sep-01	first	Muscular weakness (Nervous)	F	73.5	0	-3.29 (5.94)	-0.045

Appendix 4.1: Characteristics of drugs and DHPCs *(continued)*

DHPCs without significant long-term changes in use											
Drug Characteristics				DHPC Characteristics				Drug use		DHPC impact	
INN (ATC)	Appr. date	Initial prescriber	Inno-vativeness	DHPC date	First/ Repeated DHPC	Safety issue (SOC)	Type of serious safety issue	Median Rx before	Trend	Change in new drug use	
										Absolute (SE)	Relative
tenofovir[1] (J05AF07)	Feb-02	S	4	Jul-03	first	Drug effect decreased (General)	O	97.5	↓	20.09 (20.21)	0.206
tenofovir[2] (J05AF07)	Feb-02	S	4	Oct-03	repeat	Drug effect decreased (General)	O	97.5	↑	-27.70 (20.23)	-0.284
tenofovir[3] (J05AF07)	Feb-02	S	4	Mar-05	repeat	Drug effect decreased (General)	H	137	0	-1.36 (20.21)	-0.010
tenofovir[4] (J05AF07)	Feb-02	S	4	Mar-06	repeat	Renal disorder (Renal)	D	167.5	↑	27.33 (20.30)	0.163
nevirapine (J05AG01)	Feb-98	S	4	Feb-04	repeat	Skin reaction (Skin)	F	86.5	0	3.03 (7.30)	0.035
imatinib mesilate[1] (L01XE01)	Nov-01	S	4	Mar-05	first	Urinary bladder adenoma (Renal)	O	37.5	↑	7.06 (7.02)	0.188
imatinib mesilate[2] (L01XE01)	Nov-01	S	4	Dec-06	repeat	Cardiac failure (Cardiac)	H	53.5	0	-10.53 (7.66)	-0.197
hydroxycarbamide (L01XX05)	Nov-72	S	3	Dec-05	first	Cutaneous vasculitis (Skin)	D	133	0	6.19 (4.93)	0.047
letrozol (L02BG04)	Jan-97	S	1	Dec-05	first	Maternal drugs affecting fetus (Injury)	D	240.5	↑	33.33 (19.43)	0.139
mycophenolate mofetil (L04AA06)	Feb-96	S	4	Nov-07	first	Maternal drugs affecting fetus (Injury)	D	274	0	-7.78 (14.88)	-0.028

Appendix 4.1: Characteristics of drugs and DHPCs *(continued)*

DHPCs without significant long-term changes in use											
Drug Characteristics				DHPC Characteristics				Drug use		DHPC impact	
INN (ATC)	Appr. date	Initial prescriber	Inno-vativeness	DHPC date	First/ Repeated DHPC	Safety issue (SOC)	Type of serious safety issue	Median Rx before	Trend	Change in new drug use	
										Absolute (SE)	Relative
sirolimus (L04AA10)	Mar-01	S	1	Feb-03	first	Bronchial anastomosis complication (Respiratory)	F	6.5	0	4.66 (2.67)	0.717
etanercept (L04AB01)	Feb-00	S	4	Feb-03	repeat	Infection (Infections)	H	28	↑	-1.14 (23.31)	-0.041
celecoxib[2] (M01AH01)	May-00	GP	1	Feb-05	repeat	Cardiovascular disorder (Cardiac)	H	11851.5	0	441.44 (798.52)	0.037
botulin a toxin (M03AX01)	Dec-93	S	4	Jun-07	first	Muscular weakness (Nervous)	F	25	↑	-0.75 (5.04)	-0.030
lamotrigine[1] (N03AX09)	Jan-96	S	3	Oct-05	first	Drug effect decreased (General)	O	688	↑	51.43 (35.65)	0.075
topiramate (N03AX11)	Jun-99	S	3	Oct-01	first	Oculomucocutaneous syndrome (Eye)	D	142	0	-6.84 (40.99)	-0.048
levetiracetam (N03AX14)	Sep-00	S	3	Nov-07	first	Incorrect dose administered (Injury)	O	701	↑	38.50 (22.21)	0.055
paroxetine[1] (N06AB05)	Jun-91	GP	2	Jan-06	first	Maternal drugs affecting fetus (Injury)	D	10451	0	432.11 (713.28)	0.041

Appendix 4.1: Characteristics of drugs and DHPCs *(continued)*

DHPCs without significant long-term changes in use											
Drug Characteristics				DHPC Characteristics				Drug use		DHPC impact	
INN (ATC)	Appr. date	Initial prescriber	Inno-vativeness	DHPC date	First/ Repeated DHPC	Safety issue (SOC)	Type of serious safety issue	Median Rx before	Trend	Change in new drug use	
										Absolute (SE)	Relative
venlafaxine (N06AX16)	Dec-97	GP	1	Sep-03	first	Suicidal ideation (Psychiatric)	O	4222.5	0	443.36 (288.97)	0.105
galantamine (N06DA04)	Jul-03	S	2	Oct-05	first	Death (General)	F	232	↑	-17.31 (29.42)	-0.075
salbutamol (R03AC02)	Dec-73	GP	4	May-07	first	Myocardial ischaemia (Cardiac)	H	53595.5	0	-6126.38 (3744.96)	-0.114

* The two DHPCs issued for nelfinavir were issued close in time and were therefore treated as a single intervention and analysed together. The first DHPC was taken as the time point of intervention. **Legend: DHPC:** Direct Healthcare Provider Communication; **INN:** International Proprietary Name: drugs with more than one DHPC in our study period are indicated by their superscript numbers; **ATC:** Anatomical Therapeutic Chemical; **Appr. Date:** Approval date; **Initial prescriber:** S = medical specialist, GP = general practitioner; **Innovativeness:** 4 = important, 3 = moderate, 2 = modest, 1 = mere pharmacological/technological; **SOC:** System Organ Class; **Type of serious safety issue:** F = Death (fatal), H = Hospitalization, D = Disability/Incapacity, O = other; **Rx:** Medical prescription. **Median Rx before** = median number of Rx in the 12 months pre-DHPC; **Trend** = Trend in use pre-DHPC: ↑ = increasing, 0 = unchanged, ↓ = decreasing; **Absolute change in new drug use** = Change in absolute number of new drug use as determined through interrupted time series analyses; **SE**: standard error (of coefficient of Absolute change in new drug use); **Relative change in new drug use** = Absolute change in new drug use divided by the Median Rx before (Outcome measure).

APPENDIX 4.2: REGRESSION MODEL

Our regression model is given by

$$\begin{aligned}\Delta DrugUse_i = \; & \beta_0 + \beta_1 \times \text{Time to DHPC}_i + \beta_2 \times \text{Trend\_no}_i + \beta_3 \times \text{Trend\_dec}_i \\ & + \beta_4 \times \text{Innov}_i + \beta_5 \times \text{Specialist Drug}_i + \beta_6 \times \text{Repeat}_i + \beta_7 \times \text{Template}_i \\ & + \beta_8 \times \text{Death}_i + \beta_9 \times \text{Hospital}_i + \beta_{10} \times \text{Disabil}_i + \varepsilon_i\end{aligned} \tag{4.1}$$

where $i = 1, \ldots, 58$ representing the ith drug & DHPC pair.

In the above equation, $\Delta DrugUse_i$, the dependent variable, represents the relative change in new drug use, which is calculated as the absolute change in drug use divided by the median drug use in the 12 months before the DHPC. Time to DHPC_i specifies the elapsed time in months from drug approval to the publication of the DHPC; Trend_no_i and Trend_dec_i represent, respectively, no change and decreasing trend in use before the DHPC; Innov_i stands for the drug's degree of therapeutic innovation; Specialist Drug_i indicates whether a specialist is required for initial prescription(=1) or not (=0); Repeat_i indicates whether it is a first DHPC (=0) or whether another DHPC has been sent previously (=1). The availability of a DHPC template is denoted by a dummy variable Template_i (=1, for DHPCs sent after January 2007); and Death_i, Hospital_i, and Disabil_i represent the type of serious safety issue with death, hospitalization, and disability/incapacity, respectively. A detailed description of all variables is presented in section 4.2.2.

To account for violations to the assumptions of homoscedastic error terms we use weighted least squares (WLS) to estimate the parameters of our regression model.[17] This involves weighting the observations inversely by the amount of uncertainty in order to arrive at more efficient estimates. The idea behind this approach is that observations with smaller variances (and thus more accurate information) are given larger weights and vice versa.

Mathematically, the WLS estimator results from minimizing the equation:

$$\sum_i (y_i - \beta_0 - \beta_1 x_{i1} - \ldots - \beta_k x_{ik})^2 / h_i \tag{4.2}$$

[17] We refer to Greene (2008) for a technical derivation of the WLS estimator.

Practically, the following transformed model is estimated:

$$\frac{y_i}{h_i} = \beta_0 \frac{1}{h_i} + \sum_{k=1}^{k} \beta_k \frac{x_{ik}}{h_i} + \frac{\varepsilon_i}{h_i} \tag{4.3}$$

where the weights are given by $w_i = \frac{1}{h_i}$. In our case, the weights are the inverse of the standard deviation of the standardized effect size.

Part III

Chapter 5

Marketing new pharmaceuticals: which doctors should be detailed? And when?

5.1 INTRODUCTION

The importance of product innovation in today's dynamic and complex business environment is well recognized. New drug innovations are crucial drivers of growth in the pharmaceutical industry, both in terms of revenues and long-term profitability (Stremersch and van Dyck 2009). Innovative drugs are also important from the patient's point of view: they should lead to better quality of care and significant benefits when they fill unmet medical needs.

In the current climate of pressure on healthcare budgets, expiring patents for blockbuster drugs, and increased competition, it is important for manufacturers to understand and optimize the adoption and diffusion of new drugs, thereby shortening the time to recover the high research and development investments (Sorescu et al. 2003). Drug innovation success depends on many factors, but critical determinants are how fast the new product is adopted and by how many physicians. In this regard, three issues are of particular importance to investigate (Manchanda et al. 2005): First, not all physicians will adopt a new drug immediately or prescribe it in the same way; rather there will be some heterogeneity in drug adoption across physicians depending on needs, preferences or different physician-specific characteristics. Second, since firms utilize considerable marketing resources on promoting novel drugs, understanding how individual physicians respond to marketing efforts, and in particular to detailing, is crucial. More profound insights into these effects are needed to

target physicians more effectively. Third, heterogeneity is also observed over time because decisions may differ between trial and repeat prescribing of a newly launched drug.

Although there is an increasing interest in studying pharmaceutical innovation diffusion, little research has been conducted that combines the three different sources of heterogeneity within one framework. This research gap has also been highlighted by Peres et al. (2010) who called for research that brings together individual-level adoption decisions and macro-level diffusion and develops models that help to understand the relative roles of initial adoption and repeat purchase in the diffusion process.

In this chapter, we study how the interplay between stage in the adoption process, marketing efforts, and physician characteristics affect new drug prescriptions as there is an increasing need to better understand why and how new products are accepted differently. Knowledge about which physicians are most sensitive to marketing actions and when they are most receptive will help marketing efforts to be targeted more effectively. To this end, we modify an existing framework from the diffusion model literature to study individual-level adoption by physicians.

We follow the prescription history of a large panel of UK physicians and investigate their first and subsequent prescriptions for a new-to-the-world drug that was launched in the antidepressant category. An important feature of our database is that it contains the complete detailing history of each of the physicians over the study period. Coupled with information on various characteristics of the physicians such as age, geographical location, and practice size, these single-source data allow for an unprecedented level of detail in our analyses.

Our methodology uses a nonhomogeneous Markov chain model to describe the transitions between the different adoption stages. Hierarchical Bayesian procedures are employed for modeling and estimating individual-level parameters. This approach also allows us to address the potential issue of simultaneity/endogeneity arising from the possible dependence between physicians' intrinsic propensity to adopt and targeted detailing (Liu and Gupta 2012a).

Our study makes the following contributions: First, we explicitly examine the impact of detailing efforts and physician characteristics on the intrinsic propensity to progress through the different stages of the adoption process. Second, we develop a methodology which provides guidance on which physicians should be approached with detailing efforts in the different stages of the adoption process. Our approach allows for dynamic targeting strategies depending on the last (observed) behavior of the physician. We establish that taking into account the different stages of the adoption process helps improve physician targeting.

This chapter is organized as follows: In the next section, we discuss our conceptual framework. Section 5.3 describes the data. In the subsequent section, we present the modeling approach and the Hierarchical Bayesian estimation procedure. In section 5.5, we report our empirical results. We discuss the implications of our findings and establish their managerial relevance by means of scenario analyses in section 5.6. In section 5.7, we present our conclusions and we discuss limitations and opportunities for further research.

5.2 CONCEPTUAL FRAMEWORK

Modeling the adoption and diffusion of new products has a long history in marketing research. One of the earlier and most influential models in this research stream is the Bass model (Bass 1969). Over the years, numerous extensions have been developed in order to overcome the limitations of these early diffusion models. Examples include: trial-repeat diffusion models and the explicit incorporation of marketing mix variables and network effects. All these extensions provide a better representation of reality (for an overview, see Peres et al. 2010).

Recent examples of diffusion modeling outside the pharmaceutical arena include a study by Peers et al. (2012) that incorporates seasonality in the diffusion process. A study by Ho et al. (2012) examines the effect of social contagion on the timing of new product adoption and customer value. Their proposed framework is able to quantify the value of a customer (which is the sum of the customer's purchase and influence value) in the diffusion process where social contagion is important.

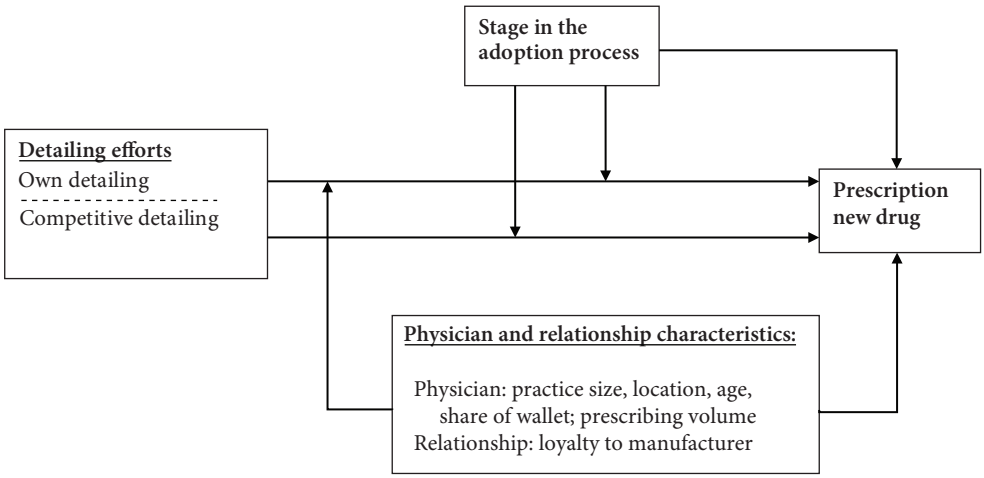
Prior research into pharmaceutical diffusion that includes trial and repeat usage of a new pharmaceutical product include Lilien et al. (1981) and Mahajan et al. (1983) who apply a trial-repeat diffusion model on two segments, prescribers and non-prescribers. Hahn et al. (1994) propose a four-segment trial and repeat model and test it on a large set of drug and therapeutic classes. Ruiz-Conde et al. (2009) extend the model by Hahn et al. by separating the effects of own and competitive marketing. However, these studies focus on the aggregate level. Since adoption decisions generally take place on a disaggregate level, scholars increasingly emphasize the need to account for individual-level predictors (Muller et al. 2009; Peres et al. 2010).

Drawing from prior research, we identify three types of factors that influence new drug prescriptions. These are: pharmaceutical marketing efforts, physician-specific characteristics, and the different stages of the adoption process (Glass and Rosenthal 2004; Montoya et al.

2010; Narayanan et al. 2005). We summarize the relations between these groups of factors and prescription behavior in our conceptual model (Figure 5.1).

In this section, we discuss the different factors and their potential effects on new prescriptions. We first discuss the direct effects of the stage in the adoption process, marketing efforts, and physician and relationship characteristics on prescription behavior and subsequently consider possible interactions.

Figure 5.1: Conceptual model of direct and moderating effects on prescriptions



5.2.1 Direct effects of stage in the adoption process

Immediately after introduction, the rate of new prescriptions for the new drug tends to start slowly (Rogers 2003). Physicians lack sufficient knowledge about the new drug's efficacy to make an informed decision about prescribing the innovation. The propensity to try and the consequent repeat rates are low; the product needs to 'take off'. When new clinical evidence and the experiences from early adopters become available, more physicians will become aware and interested in the new product and the product may 'take-off' and grow quickly. Over time, physicians learn about the drug's efficacy and side effects through different information sources such as patient feedback and/or discussions with professional colleagues, and they incorporate this information in their decision (e.g., Camacho et al. 2011; Chintagunta et al. 2009). Hence, the probability of prescribing the new drug increases. At the end of the product life cycle new alternatives with superior benefit-risk profiles and generics become available,

and probability of prescribing the once innovative drug decreases (Hahn et al. 1994; Rogers 2003).

We conclude that the stage of the adoption/diffusion process exerts a direct influence on prescription behavior.

5.2.2 Direct effects of pharmaceutical marketing

Innovative prescription drugs require marketing support to ensure successful adoption. It is therefore not surprising that pharmaceutical companies spend the majority of their marketing budgets in the first two years following launch (Osinga et al. 2010). Primarily, marketing activities are directed at physicians through visits from sales representatives (also known as detailing), drug samples, meetings and symposia, as well as medical journal advertising.

5.2.2.1 Own detailing efforts

The substantial amount that pharmaceutical companies spend on promoting their products has led to an extensive debate about the desirability of pharmaceutical marketing activities. Consequently, much scholarly attention has been devoted to studying the impact of detailing efforts on prescribing behavior and pharmaceutical demand, but evidence is inconclusive about the direction and size of the effect of own detailing efforts (e.g., Fischer and Albers 2010; Gönül et al. 2001; Kremer et al. 2008; Leeflang and Wieringa 2010; Manchanda and Chintagunta 2004; Manchanda and Honka 2005; Mizik and Jacobson 2004; Narayanan and Manchanda 2009). Most studies find positive and significant effects of detailing, but some studies report that the effects can be zero or even negative (Leeflang and Wieringa 2010; Rosenthal et al. 2003). Regarding the size of the effect of detailing efforts some authors find a strong effect on prescribing behavior while others find only modest effects (e.g., Kremer et al. 2008; Leeflang and Wieringa 2010; Wieringa and Leeflang 2013).

5.2.2.2 Competitive detailing efforts

Competitive detailing effects have been less frequently studied, usually due to a lack of data. In general, competitive marketing activities negatively influence own demand/sales. This has also been confirmed for prescription pharmaceuticals in studies by, for example, De Laat et al. (2002) and Windmeijer et al. (2005). Also Dong et al. (2011) and Leeflang and Wieringa (2010) report a negative effect of competitive detailing on prescriptions. Dong et al. study multiple categories and find heterogeneity in competitive detailing effects within and across categories.

5.2.3 Direct effects of physician and relationship characteristics

The role of individual physician and relationship characteristics on adopting and prescribing new pharmaceuticals has been discussed in both the medical and marketing literature (e.g., Glass and Rosenthal 2004; Greving et al. 2006; Janakiraman et al. 2008; Manchanda et al. 2008; Narayanan and Manchanda 2009). The adoption of new drugs varies for example by age, gender, practice size (i.e., number of practitioners), or the physician's relationship with the pharmaceutical manufacturer.

Prior research suggests that younger physicians are more likely to prescribe new drugs earlier (than older colleagues) as are male physicians when compared to their female counterparts (e.g., Glass and Rosenthal 2004; Steffensen et al. 1999). Mixed results have been found with regard to practice size. Some previous studies report a positive association between practice size and adoption (Steffensen et al. 1999; Williamson 1975) while others report the opposite (Greving et al. 2006). Some studies have also looked at whether physicians' practice location affects their adoption behavior (Greving et al. 2006; Manchanda et al. 2008). Moreover, physicians' pre-launch prescribing volume appears to influence new drug adoption. Glass and Rosenthal (2004) find evidence of significant effects of total prescribing volume on both the adoption of first-in-class drugs and follow-on drugs. It has been shown that heavy prescribers are more likely to innovate and also receive more detailing calls so that heavy category prescribing physicians are expected to have a higher trial probability (e.g., Glass and Rosenthal 2004; Manchanda et al. 2004; Rogers 2003). This proposition receives support from research on new products in general. Consumers who display high category usage levels have a greater category need and therefore a higher adoption probability for a new product within that category (Gatignon and Robertson 1991). Studies further point out that past response to innovation adoption and familiarity (total prescribing volume within the drug class) are important predictors of new (follow-on) drug adoption (Glass and Rosenthal 2004; Kamakura et al. 2004). In addition, certain intrinsic personality characteristics may influence a physician's innovation adoption behavior (e.g., Oren and Schwartz 1988).

The physician's relationship with a pharmaceutical company may also affect prescribing behavior. It has been suggested that novel drug adoption likelihood increases when a physician is more loyal (i.e., has a high share of prescriptions from the innovating company; Glass and Rosenthal 2004). Moreover, the product information doctors receive from pharmaceutical companies may establish a brand loyalty effect that persists even after patents expire (Dalen et al. 2011). In addition, branded drugs are still often perceived of having higher quality than their generic counterparts which can lead to the creation of loyalty towards the

brand or manufacturer (Frank and Salkever 1992). Stronger loyalty for brand-name drugs has been observed for more price-insensitive physicians (Lundin 2000).

5.2.4 Indirect effects / Interactions

Pharmaceutical detailing is an important means of providing information about the new drug and eventually influencing prescription choice. The detailing information provided by the manufacturer of the new product may reduce the physician's uncertainty about the actual quality of the drug. Yet, in later stages physicians become more familiar with the product, and detailing is mainly aimed at creating market power. Narayanan et al. (2005) suggest that in the adoption/trial phase of a new drug, detailing is an important source of information while in subsequent life cycle stages detailing merely serves as a reminder to influence preferences through goodwill accumulation. This relates to the informative versus persuasive role of marketing communication (Hurwitz and Caves 1988; Leffler 1981) and is supported by more recent research (Ching and Ishihara 2012; Narayanan and Manchanda 2009). In an effort to disentangle the two roles, Ching and Ishihara (2012) studied the ACE-inhibitor market and find that the informative role is mainly chemical specific and responsible for the diffusion at the chemical level. The persuasive role, in contrast, is accountable for the brand switching behavior for brands that contain the same chemical. Osinga et al. (2010) find that the persistence of marketing effects depends on the stage of the product life cycle. These effects are strongest around the introduction of a new product and then decline in size over time.

We conclude that detailing is unlikely to be equally effective throughout the product life cycle. Consequently, stage in the adoption process may affect prescription behavior indirectly via time varying effectiveness of detailing efforts.

A second indirect effect that we include in our model is the interaction between physician characteristics and marketing efforts. Previous research has demonstrated that physicians differ in their responsiveness to pharmaceutical marketing communication (Camacho et al. 2011; Manchanda and Chintagunta 2004; Montoya et al. 2010; Narayanan and Manchanda 2009; Venkataraman and Stremersch 2007). For example, the effects of marketing vary with demographic characteristics such as gender or age, and also factors such as a physician's specialty or practice size (e.g., Janakiraman et al. 2008; Manchanda et al. 2004). Studies indicate that specialist prescribers or single-practice physicians are more receptive towards detailing than their primary care colleagues or physicians in multi-partner practices (Manchanda and Chintagunta 2004; Strickland-Hodge and Jeqson 1980). Furthermore, physicians tend to have certain (intrinsic) brand preferences independent of external factors such as price and promotion (Dong et al. 2009; Gönül et al. 2001).

5.3 BACKGROUND AND DATA OVERVIEW

We empirically investigate the interplay between stage in the adoption process, marketing efforts, and physician characteristics using data from the antidepressants category. Before we turn to the modeling approach, we provide some background information on the antidepressant market and describe our data.

5.3.1 Antidepressants

Depressive disorders place major societal and economic burdens to economies. According to WHO projections, it will be one of the leading causes of disability in developed nations by 2020 (Mathers and Loncar 2006). Therefore, it is not surprising that antidepressants belong to the most heavily prescribed drug classes worldwide. In 2011, over 45 million prescriptions have been dispensed for antidepressants in the community in England. Recent estimates suggest that the total cost of depression to the UK economy will reach £10 billion within the next few years (NHS 2012).

Four antidepressant classes can be distinguished: (1) Tricyclic antidepressants (TCAs) and (2) monoamine oxidase inhibitors (MAOIs), both developed in the 1950s, (3) selective serotonin reuptake inhibitors (SSRIs) and (4) serotonin-norepinephrine reuptake inhibitors (SNRIs), the newer antidepressant classes. The medical literature commonly groups these classes into 'first generation' and 'second generation' antidepressants (Gartlehner et al. 2011). The drugs we focus on fall into the second generation and include SSRIs and SNRIs which share a similar mode of action. They selectively block the reuptake of serotonin or serotonin and norepinephrine—neurotransmitters that have been linked to depression, particularly a lack thereof—and thereby increase their availability for transmission of important signals in the nervous system. The second generation antidepressants are nowadays the preferred therapy in the treatment of major depressive disorders, accounting for the majority of antidepressant prescribing. Although effective for certain types of depression, first generation antidepressants (MAOIs and TCAs) have shown severe side-effects and high risk of overdose, ascribed to their non-selective effect on other chemicals in the brain.

Launched in 1989 in the UK, Prozac (marketed by Eli Lily) was the first SSRI, and a major innovation in the antidepressant market. The novel drug has been praised for its more favorable side-effects profile and better tolerability and rapidly expanded market share. Within a short period of time more SSRIs followed. Between 1991 and 2000 prescription volume for SSRIs increased almost twentyfold (Middleton et al. 2001). In the mid-1990s, the first SNRI was introduced which selectively acts upon two neurotransmitters (serotonin and

norepinephrine). SNRIs therefore have been suggested to be even more effective; however, clinical evidence of superior efficacy is mixed (Thase 2008).

5.3.2 Data

Our panel data set covers 46,841 prescriptions written by 137 UK physicians over a period from September 1st, 1988 to July 31st, 1997.

During the observation period, six new drugs were launched onto the UK market:

1. Prozac (fluoxetine) was the first molecule of a new generation of antidepressants (SSRIs) and launched in January 1989.
2. Lustral (sertraline), the first me-too, was launched in December 1990.
3. Seroxat (paroxetine), the second me-too, was launched in March 1991.
4. Effexor (venlafaxine), the first SNRI, was launched in January 1995.
5. Dutonin (nefazodone), also an SNRI, was launched in April 1995 (and later withdrawn).
6. Cipramil (citalopram), a newer SSRI, followed shortly after in August 1995.

The focal brand in our study is Prozac, the first among the SSRIs introduced in the UK market which was radically innovative. Seroxat, marketed by GlaxoSmithKline, is Prozac's main competitor in terms of number of prescriptions in our dataset.[18] For parsimony, we group the remaining competitors in one category: 'other (competing) products'.

Our dataset contains all prescriptions of all physicians who wrote at least one prescription (for any drug, in any category) in at least 10 of 52 weeks in each year covered by the data subset. This provides us with continuous data and obviates problems of panel attrition. All physicians in our sample are general practitioners (GPs).

Along with information on prescriptions written for all competitive molecules the data collected at the individual level comprise detailing information (i.e., date of detailing visit and drug detailed) about the focal drug and the key competitor drugs in the marketplace. Both the median number of detailing calls per doctor for the focal brand and the median number of competitive calls in the six month preceding a prescription is one. The maximum number of detailing calls in the six month preceding a prescription amounts to 14 for the focal product; the maximum number of competitive calls is 18. We further have physician-specific information which includes age, size of practice, and practice geodemographics.

[18] This has been also confirmed by a study on antidepressant use in general practice in the UK which finds Seroxat to be second among the SSRIs with respect to prescribing volume (Lawrenson et al. 2000).

5.4 MODEL DEVELOPMENT

Our approach is motivated by the desire to accommodate the different stages in the adoption/diffusion process when examining the individual-level adoption behavior of physicians. A Markov setting is the natural choice for modeling transitions between different stages (e.g., Ding and Eliashberg 2008; Montoya et al. 2010, Netzer at al. 2008; Sung et al. 2007). Such a model allows us to study trial and repeat patterns as well as brand switching dynamics. In a recent study, Montoya et al. (2010) employ a hidden Markov model (HMM) to account for the dynamics in physician prescription behavior of newly introduced drugs. A HMM is a stochastic process that is not directly observable, but can only be observed through another set of stochastic processes that produces a sequence of observations (Rabiner and Juang 1986). Hence, HMMs consist of two types of states, observable and unobservable ('hidden') states, for which the underlying process is a Markov chain process. Our set-up is different from Montoya et al. (2010) in that we observe at each prescription occasion the state a physician is in. Using a hidden Markov approach would require that we incorporate an additional layer which would inevitably complicate the model and come at the cost of tractability. We therefore choose to investigate physician characteristics on these observed states.

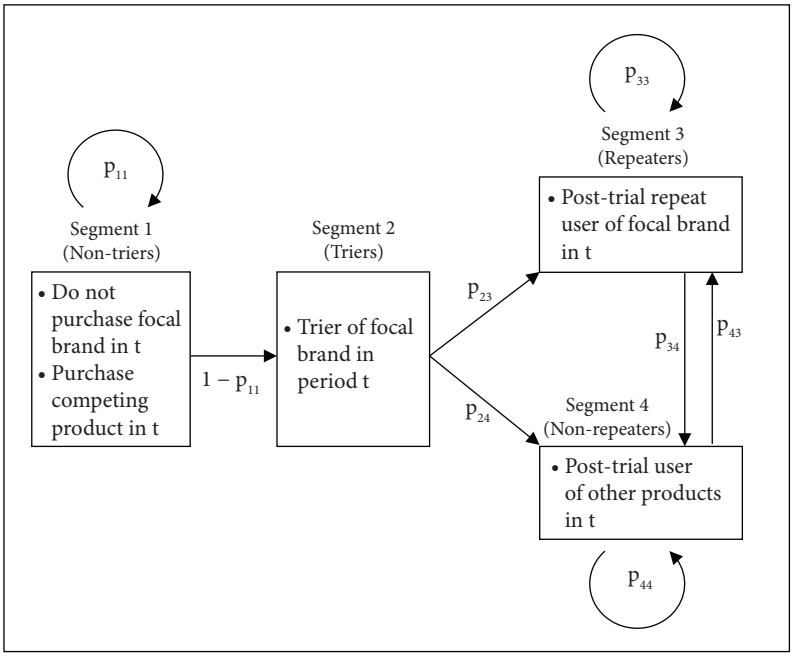
In developing our model we draw on diffusion models that have been applied in pharmaceutical marketing research and explicitly consider physicians to be in different stages in the diffusion process of a new prescription drug (e.g., Hahn et al. 1994; Lilien et al. 1981; Mahajan et al. 1983). In this respect, the models of Lilien et al. and Mahajan et al. incorporate two segments (prescribers and non-prescribers) whereas the model of Hahn et al. proposes four segments (nontriers, triers, posttrial nonrepeaters, and posttrial repeaters), which makes it particularly interesting for this study. Their framework is presented in Figure 5.2. For reasons discussed below we will modify the model of Hahn et al. (1994, hereafter HPKZ model).

Our starting point is the four-segment HPKZ model. Their framework provides a natural way of specifying the dynamics in the different stages of the adoption process. Later, we specify how we include marketing efforts and physician characteristics.

HPKZ classify physicians into four segments depending on where they are in the adoption process. The first segment consists of physicians that have not tried the new product; the second segment contains those physicians that have tried the new product only once. The third segment comprises those physicians that repeat the use of the innovation. The physicians who have tried the innovation but then used a competing product and not repeated their use of the innovation constitute the fourth segment. As a consequence of this definition of

segments, physicians can neither switch back to the first segment (non-triers) if they have ever tried the product (segment two) nor can they go back to the second segment (triers of the innovation) if they were in segment three or four.

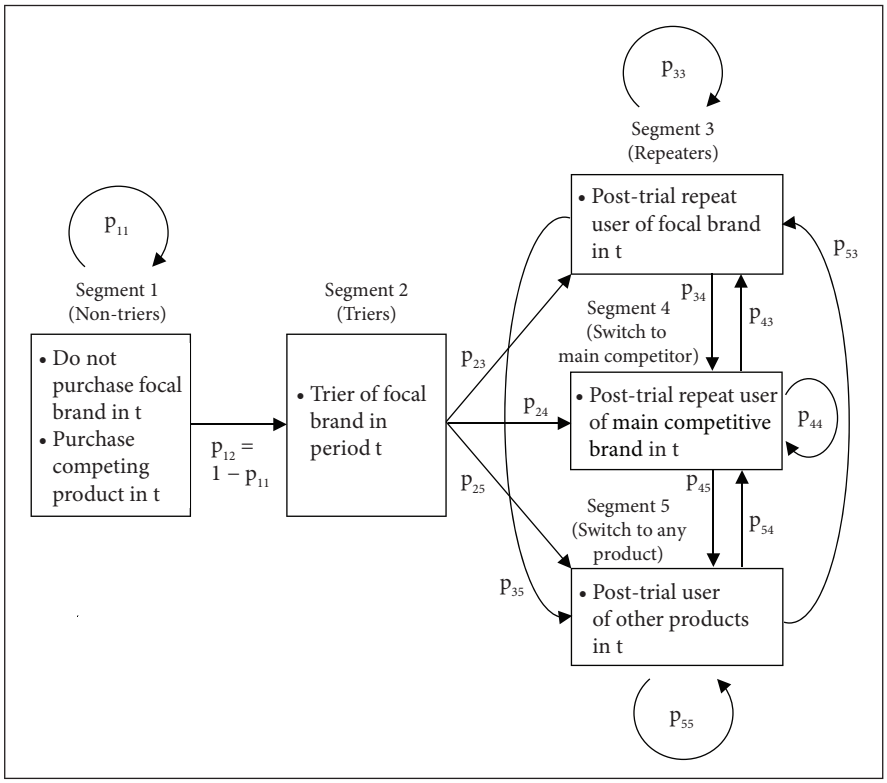
Figure 5.2: HPKZ framework



adapted from Hahn et al. (1994)

To be able to distinguish between switching behavior to the main competitor and other competing products, we cannot apply the HPKZ framework directly and extend the four-segment model by one additional segment. Basically, our extended model splits the non-users of the focal brand in the original HPKZ model into two groups: the post-trial users of the main competitive brand and the post-trial users of other products (that are neither the focal nor the main competitor brand-name product). We present the five-segment framework and the possible transitions between the segments in Figure 5.3.

Figure 5.3: Extended HPKZ framework



5.4.1 Markov chain model

In order to include the marketing effort variables and the physician characteristics, we specify an individual-level nonhomogeneous Markov model in which the Markovian transitions are a function of these covariates. Our model is inspired by Sung et al. (2007) who propose a logistic regression set-up for describing patient transitions among different psychiatric treatment states. Compared to their model, we include a hierarchical structure to capture the nature and determinants of heterogeneity.

Let $\{s_{m0}, s_{m1}, ...,s_{mt},...,s_{mT}\}$ be a sequence of random variables with finite state space $(1,...,J)$ where s_{mt} is defined as the state of physician m at prescription occasion t. As shown in our extended HPKZ framework (Figure 5.3), there are five states that a physician can occupy, hence $J = 5$. The transition of physician m at prescription occasion t is captured by the variable x_{mijt}, where $x_{mijt} = 1(s_{mt} = j | s_{m,t-1} = i)$, where 1(A) is an indicator function that takes the value 1 if event A occurs, else it takes the value 0. We assume that the vector $x_{mit} = (x_{mi1t},..., x_{miJt})$

follows a multinomial distribution with prob ability vector $\pi_{mit} = (\pi_{mi1t},\ldots, \pi_{miSt})$, where $\pi_{mijt} = p(s_{mt} = j|s_{m,t-1}=i)$ are the transition probabilities defined at the individual level of physician m, and $\Sigma_j\pi_{mijt} = 1$ (cf. Sung et al. 2007). The multinomial model for the transitions from state i can be formulated as: $(x_{mit}|\ \pi_{mit}) \sim Multinomial(\pi_{mit},1)$ for $i, j = 1,\ldots,J$; $t = 1,\ldots,T$; $m = 1,\ldots,M$.

We define Π_{mt} as the matrix of transition probabilities for physician m. Given our five-segment framework (Figure 5.3), Π_{mt} is written as:

$$\Pi_{mt} = \begin{bmatrix} \pi_{m11t} & \pi_{m12t} & 0 & 0 & 0 \\ 0 & 0 & \pi_{m23t} & \pi_{m24t} & \pi_{m25t} \\ 0 & 0 & \pi_{m33t} & \pi_{m34t} & \pi_{m35t} \\ 0 & 0 & \pi_{m43t} & \pi_{m44t} & \pi_{m45t} \\ 0 & 0 & \pi_{m53t} & \pi_{m54t} & \pi_{m55t} \end{bmatrix} \tag{5.1}$$

5.4.2 Specification of transition probabilities

Next we describe how the transition probabilities in (5.1) depend on marketing variables and physician characteristics. We follow a Hierarchical Bayesian setup, because we assume that the effects of time-dependent covariates are nested in physicians. In this model we have specifications at two levels.

At level 1, we apply a multinomial logit transformation to relate the time-dependent covariates to the nonzero transition probabilities in (5.1) (cf. Sung et al. 2007), i.e., for $\{i, j \mid 1 \le i \le J, 1 \le j \le J, \pi_{mijt} > 0\}$:

$$\pi_{mijt} = \text{Prob(transition from state } i \text{ to state } j) = \frac{\exp\left(F_{mt}\theta_{mij}\right)}{\sum\limits_{\{j|1\le j\le J,\ \pi_{mijt}>0\}} \exp\left(F_{mt}\theta_{mij}\right)}, \tag{5.2}$$

where F_{mt} is a vector of time-varying covariates for the mth physician, containing own and competitive detailing, and θ_{mij} is the corresponding parameter vector. For identification purposes, we define for each i a baseline category b_i, for which $\theta_{mib_i} = 0$. This leaves us with nine transition probabilities to estimate (cf. equations 5.1 and 5.2) and hence nine relevant parameter vectors θ_{mij}.

Specifically, we express our transition probabilities π_{mijt} for $\{i, j | 1 \le i \le J,\ 1 \le j \le J,\ \pi_{mijt} > 0\}$ as:

$$\pi_{mijt} = \frac{\exp\left(\theta_{1mij} + \theta_{2mij} \times DET_{mt} + \theta_{3mij} \times CDET_{mt}\right)}{\sum_{\{j | 1 \le j \le J,\ \pi_{mijt} > 0\}} \exp\left(\theta_{1mij} + \theta_{2mij} \times DET_{mt} + \theta_{3mij} \times CDET_{mt}\right)}, \tag{5.3}$$

where DET_{mt} denotes own detailing effort, which is the number of detailing calls a physician received for the drug during six month preceding prescription occasion t, and $CDET_{mt}$ denotes competitive detailing calls received during six month preceding prescription occasion t.[19,] Because we do not expect any forgetting to occur within the six month period preceding the prescription, we do not specify a decay function, but take the sum of the previously received detailing calls[20]. The intercept parameter θ_{1mij} determines the intrinsic propensity of physician m to switch from state i to state j. The parameters for the time-varying covariates (θ_{2mij} and θ_{3mij}) are allowed to depend on the state transition (hence the indices i and j) and the physician characteristics (index m).

At level 2 of the hierarchy, we model the effects of the physician characteristics utilizing a random-effects distribution whose mean is a function of moderating covariates (Rossi et al. 2005). In our conceptual specification we consider the following physician-specific characteristics as covariates: practice size, location of practice, age of prescriber, share of wallet, and loyalty to manufacturer.

We first discuss the specification for the θ_{1mij}'s: the intrinsic propensities to prescribe. We then turn to the specification of the θ_{2mij}'s: the effectiveness of detailing. We finalize our model development with the specification of the θ_{3mij}'s, which represent the effectiveness of competitive detailing.

Define θ_{1m} as the vector of the nine relevant θ_{1mij}'s: $\theta_{1m} = \{\theta_{1mij} \mid 1 \le i \le J,\ 1 \le j \le J,\ j \ne b_i,\ \pi_{mijt} > 0\}$. We specify for θ_{1m} the following:

$$\theta_{1m} \sim MVN\left(\mu_{\theta_{1m}}, \Sigma_{\theta_{1m}}\right) \tag{5.4}$$

where $\mu_{\theta_{1m}}$ and $\Sigma_{\theta_{1m}}$ are a mean vector and a covariance matrix of appropriate sizes (9×1, and 9×9, respectively). Specifically, for the covariance matrix $\Sigma_{\theta_{1m}}$ we use a Wishart distribution, $\Sigma_{\theta_{1m}} \sim Wishart\ (0.001 \times I, 9)$, where I is the identity matrix.

19 The index j is suppressed in DET_{mt} and $CDET_{mt}$ because the index m and t together define j.

20 For studies that do use a discounted formulation for (cumulative) detailing, see for example Gönül et al. (2001); Fischer et al. (2011); Leeflang and Wieringa (2010).

Furthermore, each element of $\mu_{\theta_{1m}}$ depends on physician characteristics:

$$\begin{aligned}\mu_{\theta_{1mk}} = \; & \gamma_{11k} + \gamma_{12k} \times PRACTSIZE_m + \gamma_{13k} \times SOW_m + \gamma_{14k} \times AGE_m \\ & + \gamma_{15k} \times LOYALTY_m + \gamma_{16k} \times REGION_m + \gamma_{17k} \times VOLUME_m\end{aligned} \tag{5.5}$$

where

k = 1,…,9;

$PRACTSIZE_m$ = Size of physician practice in terms of number of GPs working in the practice;

SOW_m = Share of wallet, which is the number of prescriptions a physician wrote in the category relative to the total number of prescription s/he wrote for any drug. This could be seen as an indicator of whether a GP is a 'specialist' in the related disease area;

AGE_m = Physician age;

$LOYALTY_m$ = Loyalty to the manufacturer of the focal brand operationalized as the average share a physician prescribes from the company of that brand;

$REGION_m$ = Dummy variable indicating whether the physician's practice is in a rural or an urban area (0 = rural, 1 = urban);

$VOLUME_m$ = Category-level prescription volume that is the (absolute) number of prescriptions written in the category; an indicator of whether a physician is a heavy prescriber.

Similarly, we model the vector of effectiveness coefficients of detailing, θ_{2m}, as

$$\theta_{2m} \sim MVN\left(\mu_{\theta_{2m}}, \Sigma_{\theta_{2m}}\right), \tag{5.6}$$

where θ_{2m}, $\mu_{\theta_{2m}}$ and $\Sigma_{\theta_{2m}}$ are defined analogously to θ_{1m}, $\mu_{\theta_{1m}}$ and $\Sigma_{\theta_{1m}}$ respectively, and where each $\mu_{\theta_{2mk}}$ (k = 1,…,9) depends on physician characteristics:

$$\begin{aligned}\mu_{\theta_{2mk}} = \; & \gamma_{21k} + \gamma_{22k} \times PRACTSIZE_m + \gamma_{23k} \times SOW_m + \gamma_{24k} \times AGE_m \\ & + \gamma_{25k} \times LOYALTY_m + \gamma_{26k} \times REGION_m + \gamma_{27k} \times VOLUME_m,\end{aligned} \tag{5.7}$$

where all variables were defined previously.

We define the effectiveness of competitive detailing, θ_{3m}, analogously to θ_{1m} and θ_{2m}. However, for parsimony reasons, we pool across physicians because we consider competitors' detailing calls as a control variable.

$$\theta_3 \sim MVN\left(\mu_{\theta_3}, \Sigma_{\theta_3}\right) \tag{5.8}$$

where the covariance matrix Σ_{θ_3} is set equal to 0.001 times an identity matrix of appropriate size.

Finally, we specify multivariate normal priors for the γ's with expected value 0 and noninformative Wishart priors for the covariances. Specifically, for each $h = 1,2$ and $r = 1,\ldots,7$, we specify the following priors: $\left(\gamma_{hr1},\ldots, \gamma_{hr9}\right)' \sim MVN\left(0, \Xi_{hr}\right)$. For all Ξ 's we specify diffuse Wishart priors of dimension 9.

5.4.3 Model estimation procedure

We estimated our model using standard Hierarchical Bayes estimation (MCMC) procedures. For a detailed exposition of these procedures we refer to e.g., Gelman et al. (2003) and Rossi et al. (2005). Draws from the joint posterior were obtained using Metropolis-Hastings and Gibbs sampling algorithms. The algorithms generate a sequence of draws where each parameter of interest is sampled conditional on the other parameters in the model. If a specific full posterior conditional distribution is of known form we can sample from this distribution. In cases where the form is unknown or where the conditional density is intractable a hybrid MCMC algorithm is a more efficient algorithm for updating (Geweke 2005).

We used WinBUGS software (Lunn et al. 2000) that implements a Metropolis-Hastings within Gibbs algorithm to sample from the posterior distribution when the full conditional distributions are not completely known.[21] After a suitable burn-in period (here: 50,000 iterations) we retained a sample of 2000 realizations to make inferences. Convergence was assessed through visual inspection of the trace plots and the method proposed by Gelman and Rubin (1992) which compares the variability within parallel chains to the variability between parallel chains.

[21] Note that the covariates were standardized by centering and normalizing based on the arithmetic mean and standard deviation before estimation to improve convergence.

5.5 FINDINGS

5.5.1 Estimation results

Our main interest lies in understanding how individual physician and relationship characteristics affect the individual physician's propensity to prescribe and her/his responsiveness to detailing in different stages of the adoption of a novel pharmaceutical product.

In what follows, we focus on the θ_1's, which can be interpreted as the basic propensity to prescribe and the θ_2's, that is, the sensitivity to detailing. Findings reported below in Tables 5.1A and 5.1B concentrate on the most interesting (from a firm's point of view) prescription stages: (initial) trial of the new drug (p_{12}), repeat usage (p_{33}), switch from the focal drug to the main competitor brand (p_{34}), and win the physician back from either the main competitor (p_{43}) or other competing drugs (p_{53}; see Figure 5.3).

We first discuss the effects of physician characteristics on θ_1, the basic propensity to prescribe, in different stages of the adoption process (Table 5.1A). We then turn to the effects of physician characteristics on θ_2, the sensitivity to detailing, in different stages of the adoption process (Table 5.1B). We discuss the results column-wise focusing on the significant findings from our analysis first. We end with a discussion on other (nonsignificant) effects.

5.5.1.1 Basic propensity to prescribe

Table 5.1A, column 2 presents the repeat rates. They are found to be significantly higher for physicians who are loyal to the pharmaceutical company, as indicated by the positive loyalty parameter.[22] We further find prescribing volume to be negatively related to repeat rates, that is, the propensity to write a repeat prescription is smaller for heavy prescribers. A possible explanation is that heavy prescribers use more different drugs. We investigated this proposition for our setting, relating the market share of the focal drug to prescribing volume. We found a negative and significant correlation (r=-.25, p<.001), indicating that heavy prescribers spread their prescriptions more across different products in the category. This is consistent with the notion that, in general, those who 'buy' more in a category use more alternatives (Twedt 1964).

The findings in column 3 suggest that doctors in smaller practices have a smaller propensity to switch. Our findings correspond with Janakiraman et al. (2008) who find physicians in smaller practices to be more persistent in their prescribing habits. This could be due to a lack of easy-to-access information which is more likely to be the case in smaller

[22] We point out that loyalty is a potential measure of the relationship between the pharmaceutical company and the physician.

practices because there are fewer professional colleagues and less intra-group contact. Also, smaller practices tend to have less heterogeneous patients; hence, it will be easier for physicians to apply simple prescribing rules which, in turn, may increase persistence.

Table 5.1: Parameter estimates for antidepressants

A: *Basic propensity to prescribe*

	Trial (p_{12})	**Repeat** (p_{33})	**Switch to main competitor** (p_{34})	**Attract from main competitor** (p_{43})	**Attract from others** (p_{53})
PRACTSIZE	0.051 [-0.103; 0.174]	0.065 [-0.095; 0.224]	0.381** [0.190; 0.570]	-0.062 [-0.222; 0.095]	0.057 [-0.101; 0.208]
SOW	-0.165 [N/A]	0.127 [-0.078; 0.319]	0.156 [-0.061; 0.368]	0.042 [-0.159; 0.252]	0.075 [-0.104; 0.257]
AGE	-0.198 [N/A]	0.021 [-0.128; 0.183]	0.030 [-0.127; 0.190]	0.101 [-0.047; 0.254]	-0.014 [-0.172; 0.147]
LOYALTY	0.389 [N/A]	0.399** [0.238; 0.588]	-0.292** [-0.456; -0.134]	0.450** [0.297; 0.606]	0.448** [0.307; 0.589]
REGION	-0.311 [N/A]	0.010 [-0.162; 0.207]	0.097 [-0.077; 0.268]	0.094 [-0.083; 0.270]	0.021 [-0.129; 0.174]
VOLUME	-0.260 [N/A]	-0.462** [-0.651; -0.256]	-0.251** [-0.454; -0.044]	-0.311** [-0.534; -0.096]	-0.341** [-0.526; -0.165]

B: *Sensitivity to detailing*

	Trial (p_{12})	**Repeat** (p_{33})	**Switch to main competitor** (p_{34})	**Attract from main competitor** (p_{43})	**Attract from others** (p_{53})
PRACTSIZE	-0.028 [-0.218; 0.148]	0.024 [-0.243; 0.322]	0.130 [-0.152; 0.412]	-0.026 [-0.256; 0.208]	0.032 [-0.165; 0.235]
SOW	0.122 [N/A]	0.291* [-0.005; 0.603]	0.149 [-0.121; 0.438]	0.217* [-0.027; 0.464]	0.197 [-0.057; 0.456]
AGE	-0.077 [N/A]	-0.134 [-0.363; 0.087]	-0.173 [-0.388; 0.056]	-0.055 [-0.386; 0.267]	-0.191* [-0.416; 0.026]
LOYALTY	-0.012 [-0.120; 0.082]	0.486** [0.238; 0.728]	-0.047 [-0.239; 0.141]	0.226 [N/A]	0.478** [0.280; 0.671]
REGION	-0.206 [N/A]	-0.135 [-0.368; 0.096]	0.111 [-0.071; 0.297]	-0.015 [-0.298; 0.265]	-0.053 [-0.297; 0.183]
VOLUME	-0.199 [N/A]	-0.374** [-0.665; -0.086]	-0.192 [-0.454; 0.053]	-0.176 [-0.431; 0.084]	-0.230 [-0.492; 0.053]

Legend: ** the 95% posterior density interval excludes zero; * the 90% posterior density interval excludes zero. Numbers in brackets represent the 95% posterior density interval; [N/A] indicates that the 95% or 90% posterior density intervals exclude zero but convergence is not achieved.

As would be expected, our results show that switching to the competitive brand is less likely for doctors who are loyal to the pharmaceutical firm of the focal brand (column 3). Also, more loyal prescribers are more likely to be attracted away from the competitor, as the results in column 4 indicate.

The negative coefficients in the VOLUME row for 'repeat' and 'switch to main competitor' (i.e., p_{33} and p_{34}, respectively) indicate that high-volume prescribers who are currently using the focal brand exhibit a lower propensity to repeat and a lower propensity to switch to the main competitor; therefore, their propensity to switch to other products will be higher.

The last column in Table 5.1A shows that loyalty to the brand manufacturer is associated with a higher propensity to switch back from drugs other than the main competitor to the focal brand. Also, low-volume prescribers are more likely to be attracted away from other drugs to the focal brand.

No association is found between physician characteristics and the propensity to try the new product (column 1). We note that convergence is not achieved for some parameters, which hampers our ability to draw conclusions for trial.

5.5.1.2 Sensitivity to detailing

Table 5.1B reports the findings for the sensitivity to detailing. The results in column 2 suggest that the effectiveness of detailing to generate repeat use is greater for doctors who are more specialized in the disease area (i.e., exhibit a higher category prescription share). 'Specialist GPs', due to their interest in the disease area, might be per se more interested in the new SSRI antidepressant and its better therapeutic profile, which might increase their willingness to initiate drug therapy with the new product (here: Prozac; Jacoby et al. 2003). Marketing communication may help to promote this process further, and those physicians may also be more sensitive to this source of information. If initial experience with the new product is positive, it is likely included in the physician's evoked set (i.e., a set of possible treatment options). Once added to their repertoire, physicians tend to prescribe the new drug repeatedly (through habit; Groves et al. 2002).

Column 2 further indicates that detailing is more effective in generating repeat prescriptions for physicians who are loyal to the pharmaceutical firm. This could be due to synergy effects of other calls or combined calls for different products from the same manufacturer.

We also find that detailing is less effective for generating repeat prescriptions for high-volume prescribers. As we discussed earlier, heavy prescribers might be more inclined

to use alternative, already existing antidepressant drugs[23] which could explain their lower responsiveness to detailing as well as the negative relationship between prescribing volume and repeat rates (see Table 5.1A).

Alternatively, heavy prescribers may be 'over-detailed'; a result of pharmaceutical practice that primarily targets physicians based on their prescribing volume. Both anecdotal evidence from practice and academic research has suggested that too many detailing visits do not increase prescribing but are counterproductive, i.e., reduce prescription levels (e.g., Gönül et al. 2001; Manchanda and Chintagunta 2004). Because detailing visits may take away time with patients, physicians may react negatively if detailing becomes excessive. The finding has important implication for pharmaceutical companies: a targeting strategy focused on heavy prescribers might lead to suboptimal allocation and should be carefully considered case by case.

Besides a positive impact on repeat rates, detailing is also more effective in winning doctors back from the main competitor when they are more specialized, as indicated by the positive coefficient of share of wallet (column 4).

The results in column 5 suggest that detailing is less effective in attracting doctors away from other drugs than the main competitor when doctors are older. Older doctors may have accumulated more experience with older (first-generation) antidepressants, and are more inclined to continue prescribing them. Yet, the effectiveness of detailing to attract physicians away from other drugs to the innovator Prozac is larger for those who are more loyal to the pharmaceutical company (of the focal brand).

In some stages, physician-specific characteristics appear to have little influence on detailing effectiveness. No significant impact on the effectiveness of detailing to generate trial is found (column 1). This may relate to slow parameter convergence which could be caused by the sparseness of detailing calls before/during trial. Hence, detailing effectiveness cannot be identified for this stage, let alone how it is influenced by physician characteristics. Similarly, we observe no significant association between physician characteristics and sensitivity to detailing with respect to switching to the main competitor (column 3).

As indicated earlier, we introduce competitive detailing as a control variable in our model. A striking observation is that the competitive detailing parameters are positive, although they show slow convergence. In general, one would expect competitive detailing to have a negative impact on (own) prescriptions. A possible explanation for this finding could be that competitors' marketing actions increase (physicians') attention to the category

[23] Note that our antidepressant subset also includes tricyclic antidepressants and monoamine oxidase inhibitors, which are already established treatments.

as a whole, and thereby create a positive spill-over effect from which all products will benefit (i.e., a market-expansion effect). This may be true when the (competitive) detailing messages explicitly emphasize the general advantages of the new SSRI drug class. There is some evidence within the diffusion literature that supports the positive influence of competition on the adoption/diffusion process of new products, in particular for relatively new categories or markets (e.g., Krishnamurthy 2000; Shankar et al. 1999).

5.5.2 Robustness checks

We specify a number of alternative models to investigate the sensitivity of the outcomes with regard to the different specifications of the models: (1) in the first alternative model we exclude prescription volume to investigate the effect of potential collinearity with the share of wallet variable. This analysis generates fairly similar estimates regarding sign and significance, alleviating this concern. (2) In a second alternative model we add an additional explanatory variable: squared detailing. This was done to account for diminishing returns to detailing (Gönül et al. 2001; Manchanda and Chintagunta 2004). For our final model we chose to exclude the squared detailing term as a consequence of high multicollinearity that was induced by including the squared term. Overall, the signs and significance of the coefficients remain similar under the alternative specifications. (3) We use a logit model with the number of detailing calls as predictor as a benchmark for evaluating the performance of our proposed approach. The scenario analysis, which we describe in section 5.6 below, shows that our approach outperforms the benchmark model.

Because physicians are commonly detailed based on their prescribing volume (Manchanda and Chintagunta 2004), an endogenous relationship between prescribing behavior and detailing is likely to arise from this targeting strategy. In our specific context, this means that if physicians are targeted based on their propensity to adopt, a dependency between random intercepts and physician-level detailing efforts would exist. Liu and Gupta (2012a) show that the endogeneity issue can be approached by modeling the random intercepts as a function of physician-specific characteristics. We use a similar specification (see Equations 5.4 and 5.5) and therefore, the endogeneity issue is likely to be mitigated. The concern may be further alleviated because we partly accommodate the endogeneity problem by looking only at earlier detailing calls. (Note that we previously defined detailing in terms of received calls during the six months prior to a prescription).

5.6 MANAGERIAL IMPLICATIONS

In this section we conduct a scenario exercise to illustrate the managerial implications of our findings.

Taking the position of a pharmaceutical brand manager, a key issue is how to effectively allocate resources (i.e. detailing visits) between physicians that vary in their responsiveness to detailing efforts. In this respect, it is not only important which physicians to target but also when (i.e., at which stage in the adoption process) to target them. For each physician, using the parameter estimates from our model, we predict the expected number of additional prescriptions, $E(\Delta Rx)_m$, physician m would prescribe had s/he been given an additional detailing visit. We assume that the firm is interested in maximizing the number of prescriptions written. Supposing that marginal costs of each prescription are zero, this is in line with the firm's profit maximization objective, because revenue (prescription) maximization then equals profit maximization (for a similar assumption, see Manchanda and Chintagunta 2004). We consider three cases which we think are most interesting from a managerial point of view: Which targeting strategy should be used (1) to stimulate trial given that a physician has not tried the (focal) product before, (2) to stimulate repeat use depending on the last observed prescription state of a physician, and (3) to attract physicians away from other products to the focal brand.

We consider five strategies for targeting physicians:

1. the selection of physicians that have so far received the most detailing calls for the innovator drug (base case);
2. a selection of physicians according to the criterion applied in pharmaceutical practice which is total category volume prescribed in the past (heavy prescriber)[24];
3. a random selection of physicians (naïve approach);
4. a selection of physicians who appeared to be most responsive to detailing according to the parameter estimates of the logit benchmark; and
5. the selection of physicians with the highest $E(\Delta Rx)_m$ as predicted by our model.

For each scenario, we assume that the pharmaceutical firm has a budget for 30 detailing visits. We choose this number because we wish the number of detailing visits to be considerably smaller than the number of physicians in our sample in order not to degenerate the allocation

[24] Specifically, physicians are binned into deciles according to their category prescription volume and hence, heavy prescriber are more heavily detailed.

problem.[25] For each of the scenarios we compute the expected (marginal) number of additional prescriptions due to the extra detailing visits. Based on those scenarios we select the respective physicians and sum their expected number of additional prescriptions. Specifically, for the base case the 30 physicians with the most detailing calls for the innovator drug are selected. Given that we know the detailing history of each physician, we can compute the amount of detailing calls each physician received and rank them accordingly. The second scenario implies the selection of those 30 physicians who exhibit the largest numbers of prescriptions in the category. For scenario 3, we randomly select 30 physicians from our pool of physicians. For scenario 4, we estimate individual logit models for each physician and pick those 30 physicians that have the highest detailing coefficient. Using the logit benchmark model, we take physician heterogeneity into account, but no differentiation is made with respect to the stage in the adoption process. Finally, for scenario 5, we select those 30 physicians whose expected number of additional prescriptions is largest. The results for the scenarios are shown in Table 5.2.

Table 5.2: Results for the scenario analysis

Expected number of additional prescriptions due to one additional detailing call				
Base case (current targeting)	**Heavy prescribers (practice rule)**	**Random selection (naïve approach)**	**Logit benchmark**	**'Our model'**
		(1) Stimulate trial		
-0.36	-0.59	-0.35	-0.49	-0.03
		(2) Stimulate repeat use		
-2.95	-5.90	-3.18	9.61	11.20
		(3) Attract from others		
-3.05	-5.31	-2.97	8.63	10.25

Negative numbers indicate here that an extra detailing call will lead to fewer prescriptions.

The scenario results show that targeting physicians based on their expected number of additional prescriptions (scenario 5) outperforms the alternative strategies, in both stimulating repeat use and attracting physicians away from competitive products. Although the logit benchmark performs reasonably well, companies can increase their profits even further when allocating their detailing efforts towards physicians whose expected number of

[25] We experimented with different numbers of detailing visits and reached similar substantive conclusions.

additional prescriptions is largest ('our model'). The current targeting strategy (base case), and most notably, the practice rule (i.e., targeting physicians based on their prescription volume) appear to be highly ineffective; they will result in fewer prescriptions.

The findings further indicate that detailing does not help in stimulating trial. This is unexpected because prior research generally suggested detailing to be particularly suited as acquisition tool (e.g., Montoya et al. 2010). A possible explanation is that for a real innovation (e.g., Prozac), a physician may be more cautious: s/he may not wish to rely on the information provided by detailing to make the decision to prescribe the new drug for the first time, but consult other sources of information. Detailing may, however, have a reinforcing role, i.e., having prescribed the new innovative drug for the first or first few times, detailing calls may reinforce the initial decision so that the physician is reassured about the decision s/he made, and s/he is therefore likely to prescribe the new drug again when the opportunity arises. Medical literature has confirmed that UK physicians (GPs) are rather conservative prescribers, and that the decision to try a new drug is often the result of a gradual process of building up knowledge from various sources, such as clinical experts and own clinical experience regarding the properties of the new drug (Jacoby et al. 2003; Jones, M.I. et al. 2001). Also, other marketing instruments, such as meetings or professional journal advertisements, may have affected trial. Besides that, scientific evidence conveyed to physician through academic articles, interpersonal contact with peers, and patient-related factors can be important in influencing physicians' decision to try the new product (e.g., Azoulay 2002; Chintagunta et al. 2012; Iyengar et al. 2011; Jacoby et al. 2003; Prosser et al. 2003). An alternative explanation for this finding may be our definition of trial.

In summary, the scenario analyses show that accounting for the stage of the adoption process as well as utilizing the individual physician level information will lead to more effective targeting and eventually generate higher profits.

Clearly, understanding which physicians to select for targeting to stimulate repeat use of the new (focal) product is of managerial relevance. In a next step we will exemplify the suitability of our approach to give real-time recommendations for more effective targeting when taking into account a physician's stage in the adoption process. For each physician we predict the expected number of additional prescriptions, $E(\Delta Rx)_m$, assuming that a) the physicians' last prescription state is the repeat stage of focal product, b) the physicians are prescribing the main competitor, or c) the physicians are prescribing other (non)branded products in the category. Let us now for example pick doctor 1. This doctor appears very interesting to target when s/he is in stage 3, because this would result in an expected number of about 3.8 additional prescriptions for the focal brand; however at another point in time,

when the same doctor is in stage 4, an extra detailing call would have less impact: her/his $E(\Delta Rx)_m$ is then just above one. Also doctor 2 should be targeted when s/he is in stage 3. For this doctor, however, the number of expected additional prescription is considerably lower compared to doctor 1. The resulting expected additional prescription is 0.9. When looking at doctor 3 the numbers suggest that this doctor should not be given a detailing call when s/he last prescribed the main competitive brand product, because this would have a negative impact on own (focal) brand prescriptions. However, an additional detailing call to doctor 3 when s/he has already repeatedly prescribed the focal brand would further enhance repeat use; the resulting $E(\Delta Rx)_m$ is two. Table 5.3 illustrates these examples.

Table 5.3: Illustrative example of individual physician selection: Consequences for targeting

	Last prescription state:		
Expected No. of additional prescriptions	**Stage 3 (post-trial repeat focal)**	**Stage 4 (post-trial repeat main competitor)**	**Stage 5 (post-trial repeat other products)**
Doctor 1	3.8	1.2	3.6
Doctor 2	0.9	0.7	0.3
Doctor 3	2.0	-0.3	1.1

Negative numbers indicate here that an extra detailing call will lead to fewer prescriptions.

5.7 CONCLUSION AND OPPORTUNITIES FOR FURTHER RESEARCH

In this study we empirically investigate the interplay between stage in the adoption process, marketing efforts, and physician characteristics. Specifically, we demonstrate the impact of physician characteristics on the intrinsic propensity to either stay or switch to different stages of the adoption process and identify which physician characteristics drive the effectiveness of marketing on diffusion. Our key findings can be summarized as follows: First, share of wallet has a positive impact on detailing effectiveness. In particular, the effectiveness of detailing to both stimulate repeat use of and induce switching to the innovator brand is larger for GP's specialized in treating depressive disorders. Second, it is noteworthy that loyalty to the pharmaceutical firm has important impact throughout the product life cycle on both the basic propensity to prescribe and the responsiveness to detailing. This is consistent

with previous findings that suggest company prescribing loyalty to be an important factor in explaining first-in-class drug adoption (Glass and Rosenthal 2004). Third, we find that high-volume prescribers are less responsive to pharmaceutical detailing compared to low-volume prescribers. As suggested by the correlation analysis, heavy prescribers happen to use more alternative (generic) products, which, in turn, may negatively affect their detailing sensitivity. The use of more alternative antidepressant treatments could further explain their lower repeat rates for the focal brand and their lower propensity to switch once they prescribe these alternative drugs.

The method we propose also considers which physicians should be approached with detailing efforts in the different stages of the adoption process. By means of scenario analyses we illustrate the importance of taking both physician level information and the adoption stage into account when allocating detailing resources. From the analyses some important findings arise: there is considerable heterogeneity across physicians in the propensity to prescribe as well as the sensitivity to detailing; and the relevance of individual physician characteristics changes during the adoption process. Managers can make use of these phenomena to formulate better targeting strategies, thereby improving detailing effectiveness.

We acknowledge that our study has several limitations. Firstly, a caveat is that we are unable to reach convergence for some of our model parameters. Presumably, our data are not sufficiently informative for all parameters which is caused by the sparseness of calls data in some stages, or the number of iterations may not have been long enough, or a combination of both. The data sparseness specifically holds for the trial stage, and we might consider extending our definition of trial and rerun the analysis. Secondly, we only look at the innovator drug of one therapeutic category, and therefore we cannot generalize our findings. It would be interesting to replicate the analysis with different focal products, and extend it to the second-generation innovator and me-too drugs. This allows identifying similarities and differences in adoption patterns not only across categories but also across drug generations, and contributes to greater generalizability of results. Thirdly, we do not explicitly account for product attributes (e.g., quality). The superiority of a drug manifests itself mostly in terms of fewer side effects or increased efficacy. It is therefore likely that (perceived) drug quality affects prescription behavior – both directly and indirectly through its positive impact on marketing efforts – and market size (see e.g., Berndt et al. 2002; Fischer et al. 2010; Venkataraman and Stremersch 2007). However, in the case of newly launched drugs evidence about true quality is limited. Adverse drug reactions may not become evident until a drug has been on market for a long time (Lasser et al. 2002; Mol et al. 2010). Hence, physicians may build their quality beliefs upon information from, among others, the pharmaceutical company (e.g., through detailing;

Narayanan and Manchanda 2009). Also, physicians may learn from patients' feedback about a drug's efficacy and side effects and incorporate this in their decision whether to prescribe the drug or not (Camacho et al. 2011; Chintagunta et al. 2012). We see future research that obtains patient-level data and looks at including these different sources of information as particularly important. Fourthly, although detailing is the main marketing instrument in pharmaceutical practice we acknowledge that other forms of direct-to-physician marketing such as free samples or medical journal advertising can affect adoption (e.g., Chintagunta et al. 2009; Liu and Gupta 2012a; Mizik and Jacobson 2004). Distinguishing between different types of detailing (i.e., individual versus group meetings, meetings in or outside surgery) could further enrich our understanding of how the type of detailing differentially affects individual adoption/prescribing behavior. Physicians' acceptance of novel drugs is also sensitive to social interaction effects (e.g., Manchanda et al. 2008; Van den Bulte and Lilien 2001). Recent evidence suggests that contagion is present in both trial and repeat, and works differently depending on the respective stage (Iyengar et al. 2012). While our data does not allow us to capture such influence, future research could further build on these findings. Possibly, one could view practice size as a rough proxy for contagion. Finally, we currently incorporate the dynamics in physicians' transition probabilities via time-dependent covariates. A further extension of our approach could incorporate time evolving parameters (see also Sung et al. 2007). Montoya et al. (2010) propose a hidden Markov approach (HMM) to capture the dynamics in prescription behavior and the long-term effects of marketing communication in the case of newly introduced drugs. For reasons of computational tractability outlined in more detail in section 5.4 we did not employ a HMM approach. Future research may look for ways that make HMM computationally tractable for these kinds of data and applications.

APPENDIX 5.1: COMPUTATIONAL DETAILS FOR SCENARIO ANALYSIS

1. Create transition probabilities

a. To create the transition probability matrices we substitute the estimated parameters into the equation

$$\pi_{mijt} = \frac{\exp\left(\theta_{1,mij} + \theta_{2,mij} \times DET_{mt} + \theta_{3,mij} \times CDET_{mt}\right)}{\sum\limits_{\{j|1\le j\le J,\ \pi_{mijt}>0\}} \exp\left(\theta_{1,mij} + \theta_{2,mij} \times DET_{mt} + \theta_{3,mij} \times CDET_{mt}\right)},$$

where all components have the previously defined meanings.

b. Let $\pi_{mijt}^{w/call}$ be the transition probabilities given an additional detailing call. Substituting the estimated parameters into the equation

$$\pi_{mijt}^{w/call} = \frac{\exp\left(\theta_{1,mij} + \theta_{2,mij} \times (DET_{mt} + 1) + \theta_{3,mij} \times CDET_{mt}\right)}{\sum\limits_{\{j|1\le j\le J,\ \pi_{mijt}>0\}} \exp\left(\theta_{1,mij} + \theta_{2,mij} \times (DET_{mt} + 1) \ + \theta_{3,mij} \times CDET_{mt}\right)},$$

we can create the transition probability matrices had there been an extra call.

2. Predict the number of prescriptions

a. Stimulate repeat

Because we know at each prescription occasion which state a physician occupies, we can use this information to determine the last observed state physician *m* is in. Let $x_m^{T_{last}}$ be the last state vector for physician *m*, a (0,1)-vector, where the element referring to the last state physician *m* occupies has the value 1 and all other elements are zero. We can then use the following relation to predict the physician-specific market shares for the next prescription: $\hat{m}_m = x_m^{T_{last}} \times \Pi_{m,T_{last}}$, where $\hat{m}_m = [\hat{m}_{1,m}, \hat{m}_{2,m}, \hat{m}_{3,m}, \hat{m}_{4,m}, \hat{m}_{5,m}]$ contains the state-specific market shares; $x_m^{T_{last}}$ is the physician-specific last state vector as defined above; and $\Pi_{m,T_{last}}$ is the corresponding transition probability matrix.

Similarly, in the case of an additional detailing call, we have $\hat{m}_m^{w/call} = x_m^{T_{last}} \times \Pi_{T_{last}}^{w/call}$, where $\Pi_{m,T_{last}}^{w/call}$ is the transition probability matrix given an additional call.

The expected change in the number of prescriptions due to the investment in an additional call on physician *m* is then computed as: $E(\Delta Rx)_m = (\hat{m}_{3,m}^{w/call} - \hat{m}_{3,m}) \times Rx_m$, where Rx_m is the number of monthly category prescriptions physician *m* wrote.

b. Stimulate trial

Given that the physician has not tried the product yet her/his 'last state' vector is in this case defined as x_m = [1,0,0,0,0]; the corresponding transition matrices are $\Pi_{m,1}$ and $\Pi_{m,1}^{w/call}$, respectively. Using the same formula as under 2 a) we can predict the physician-specific market shares for both conditions, i.e., with and without an extra detailing call. The expected change in the number of prescriptions is then $E(\Delta Rx)_m = (\hat{m}_{2,m}^{w/call} - \hat{m}_{2,m}) \times Rx_m$.

c. Attract from others

The procedure is similar to 2a), except that we assume that all physicians are in state 5. Hence, the 'last state' vector for each individual doctor is x_m = [0,0,0,0,1].

Chapter 6

General discussion

6.1 INTRODUCTION

The economic, societal, and political significance of the healthcare and pharmaceutical market is well recognized; and governments' commitment to improving the health of their citizens is reflected in the portion of national budgets allocated to health care. As developed economies increasingly face financial constraints, aging populations and technological change, alternative healthcare measures are needed to reduce costs while maintaining or even enhancing quality of care. The pharmaceutical industry plays a central role in developing and marketing new medical treatments that can improve patient outcomes. However, the large amount of money that pharmaceutical companies spend on promoting their therapies, in tandem with their relationships to policymakers and regulators, has provoked much criticism both from the general public and from academics.

Because of the importance of the healthcare and pharmaceutical market and its unique characteristics – for example, uncertain outcome of care, third party payments of healthcare services, tight regulations, and pharmaceutical industry's high R&D and promotional expenditures – the field of health and marketing has recently started to attract more scholars. This new academic interest contributes to the development of new and relevant knowledge in the field, as well as promotes interdisciplinary research between marketing and healthcare scholars (Stremersch and van Dyck 2009).

The relevance of an interdisciplinary perspective is underscored by the fact that the pharmaceutical arena is a place where various players meet and interact, attempting to reconcile the often diverging views on pharmaceutical innovation promotion, regulatory stringency, and the use of medicines. The challenges arising from these interactions have inspired the research presented in this dissertation.

Each part of this dissertation consists of one or more chapters, with each chapter reporting on a separate study and ending with a detailed conclusion and discussion. We shall not repeat these here. In what follows we will give a short summary of the key findings, put the studies in a broader perspective by outlining current challenges, and finally propose areas for future research.

6.2 SUMMARY OF FINDINGS

The three parts revolve around the central theme of pharmaceuticals. In our first study we investigate which important product-, store-, customer-, and competitor characteristics enhance OTC category sales and thus pharmacy sales performance. Two key findings arise: (1) We find that assortment and promotions are crucial determinants of pharmacy performance, and (2) the results suggest that retail store factors and location factors that are critical for traditional retailers may be less significant for retail pharmacies.

The next two studies aim to contribute to a better understanding of the effectiveness of risk minimization measures for medicinal products. The first of the two studies assesses the impact of regulatory interventions, i.e., safety warnings, on drug usage in practice. In the short-term, about half of the drugs that received a safety warning in the form of a DHPC exhibit a decrease in use while in the long-term a change in use is observed for only a third of the drugs with a DHPC. However, the results also show that in some cases a DHPC can lead to quite a substantial decrease in use. The second study in this part builds on the results of the first, and explores which drug and DHPC characteristics can affect the impact of safety warnings. Our results reveal that the specialist-status of the drug decreases the effectiveness of a DHPC. Moreover, the availability of a DHPC template and the type of serious safety issue are identified as important determinants. There are also indications that safety warnings have an accelerating effect on the use of those drugs that show an already declining trend in use pre-DHPC and may be at the end of their lifecycle.

In the fourth study we analyze the interplay between stage in the adoption process, marketing efforts, and physician characteristics on new drug prescriptions. Our objective is to gain further understandings about which physicians are most receptive to marketing

actions and when. This knowledge will also help managers target marketing efforts more effectively. We make use of a framework from the diffusion literature to study individual-level adoption by physicians. Our methodology employs a nonhomogeneous Markov chain model where the transition probabilities are governed by a Hierarchical Bayesian framework. Together the results show the presence of considerable heterogeneity across physicians both in the basic propensity to prescribe and the sensitivity to detailing. There is also evidence that the relevance of these drivers changes during the adoption process. Specifically, we find that loyalty to the pharmaceutical firm has important impact throughout the product life cycle on both the basic propensity to prescribe and the responsiveness to detailing. Moreover, high-volume prescribers seem more likely to use other products than the innovator product compared to low-volume prescribers. They also exhibit lower responsiveness to detailing efforts. Lastly, detailing is more effective in stimulating repeated use of and inducing switching to the innovator brand for GPs specialized in treating depressive disorders than for other GPs.

A compact summary of this thesis is presented in Table 6.1.

Table 6.1: Summary of this thesis

	Part I	**Part II**		**Part III**
	Chapter 2	**Chapter 3**	**Chapter 4**	**Chapter 5**
Title	Improving pharmacy store performance: the merits of over-the-counter drugs	Impact of safety-related regulatory action on drug use in ambulatory care in the Netherlands	Direct Healthcare Professional Communications, when do they have an impact?	Marketing new pharmaceuticals: which doctors should be detailed? And when?
Data	Scanner-based and survey data	Longitudinal data	Cross-sectional data	Panel data
Methodology	Hierarchical linear model	Interrupted time-series analysis	Linear regression analysis	Bayesian analysis of nonhomogeneous Markov chain
Key findings	Assortment and promotions enhance pharmacy sales performance. Traditional retail store and location factors appear to be less important in a pharmacy setting.	Safety-related regulatory actions lead to decreased usage in the short-term in ~ 50% of the cases. Long-term changes in use are found for one third of the drugs with a safety-related regulatory action.	Both drug and DHPC characteristics influence the impact of DHPCs on drug use. Specialist drug, template availability, seriousness of the safety issue, and pre-DHPC trend in use are important determinants.	Considerable variation in physicians' propensity to prescribe and their sensitivity to detailing. Loyalty, prescribing volume, and share of wallet are most important drivers. Relevance of drivers changes during the adoption process.

6.3 CURRENT CHALLENGES

6.3.1 A new era for retail pharmacies?

Retail pharmacies are a crucial part of the healthcare system; they contribute a great deal to the provision of health care and medicinal information. Over the past decades retail pharmacies have successfully evolved from distributing medicines (i.e., product-oriented focus) towards delivering pharmaceutical care[26] (i.e., patient-centered focus; van Mil 2005). Since recently, they increasingly have to cope with the effects of regulatory measures and growing competitive pressure.

Many European countries have seen considerable changes in the distribution chain of pharmaceuticals towards more liberalized and open markets. This has been particularly visible in the pharmacy business where deregulation measures have, for example, spurred the competition between pharmacies and non-pharmacy retailers selling non-prescription medicines. In light of the changing market environment, retail pharmacies need to develop new retail strategies to preserve their existence.

Naturally, a certain amount of tension exists between the pharmacy profession and commercial considerations (Hibbert et al. 2002). However, the two roles – retailer and medical professional – are not mutually exclusive, but complement each other when aligned in a responsible way. Specifically, this involves the development of a better understanding of business opportunities while at the same time upholding high standards in pharmaceutical care and acting in the customer's/patient's best interest (Harding and Taylor 2001).

In summary, new business models that combine retail and marketing capabilities with health service delivery are mandated. This can give retail pharmacies a competitive advantage, because, unlike non-pharmacy retailers, retail pharmacies have the expertise to provide adequate advice which consumers need to rely on when seeking over-the-counter medicines.

6.3.2 A new era of regulatory policy?

An important and often criticized issue in the current system of drug regulation is the lack of transparency. Although the regulatory system has seen major transitions from a largely passive system dominated by spontaneous reporting to more proactive risk management plans, as well as improvements in the exchange of information between regulators, industry, healthcare professionals and patients, there is no standardized way (yet) of evaluating the benefits and risks of pharmaceuticals; it still relies heavily upon subjectivity (Garattini and Bertele 2010; Moore and Bégaud 2010). For this reason, there is a strong call for more

[26] Pharmaceutical care deals, among others, with medication surveillance, patient counseling, and quality assurance (van Mil 2005).

openness and accountability regarding clinical trial data and evidence upon which regulatory decisions are based (Eichler et al. 2012).

The dominant risk minimization strategy today is the provision of educational material, such as DHPCs, information brochures, or specific training programs, as these are flexible enough to be easily implemented across different national healthcare systems that exist within the EU (Zomerdijk et al. 2012). However, this strategy bears some risks: the interpretation of the provided educational material is in the eye of the beholder, and a poorly presented or shiny format may be misconceived as commercial or promotional rather than risk minimization activity. Moreover, compliance can be impeded when healthcare professionals become overburdened with risk minimization requirements. Similarly, inconsistent information regarding the risk-benefit evaluation causes confusion for both patients and care providers and can eventually have a detrimental effect on risk management (Hirst et al. 2006; Traynor 2010).

Various stakeholders agree that an internationally standardized risk management program with shared information, broader involvement of stakeholder groups (e.g., regulators, pharmaceutical companies, healthcare professionals, patients, and public), better accessibility, and one that goes beyond the current emphasis on risks by addressing both benefits and risks will facilitate implementation and compliance (Raine et al. 2011).

Without a doubt, risk communication, as part of risk management, is a critical and important step towards improving drug usage and patient safety. In addition, other methods that assess drug safety and benefits such as biomarkers or health outcome models have been suggested to assist regulatory approval decisions and support postmarketing surveillance (Garrison et al. 2007). Still, it is too early to judge whether the current and upcoming risk management strategies will realize their full potential and be effective in daily practice in the long-run.

6.3.3 A new era in pharmaceutical innovation?

Pharmaceutical innovations are the backbone of the pharmaceutical industry. They not only sustain the industry's profitability; they can save a life or improve the quality and length of life. However, innovation in the pharmaceutical industry has been criticized on various fronts. High promotional expenditures and inappropriate marketing practices, the concentration of research resources on minor modifications (i.e., me-too drugs) instead of true innovations, and the high prices for new drugs without sufficient evidence of better therapeutic value have spurred mistrust towards the industry. To a certain extent, such criticism has also been considered one-sided, ignoring that the development of new drugs is a complex and risky

endeavor marked by high investments over a long time horizon and high attrition rates. To compensate, an adequate return on investment has to be ensured (e.g., Huskamp 2006; *The Wall Street Journal* 2012).

The innovation debate is surrounded by several challenges. Over the past years the large pharmaceutical companies have been experiencing a decrease in their R&D productivity. The number of new molecular entities that reach market approval has ebbed while at the same time costs have escalated. Amid these developments, many high-profile drugs have recently lost their market exclusivity, such as Lipitor (Pfizer), a statin used to treat high cholesterol, or Diovan (Novartis), an angiotensin II receptor antagonist used for hypertension, which has resulted in serious financial losses for their brand manufacturers. Once a patent expires, generic competitors quickly enter the market offering lower-priced equivalents. As a consequence, the incumbent often suffers substantive sales losses (Gonzales et al. 2008; Osinga 2011).

Meanwhile, the economic pressure on the industry to develop therapeutic innovations to maintain sufficient market share and hence profits is rising. Technological advances, new requirements in the fields of immunology and oncology, and the growing presence of biologicals will pose additional challenges to pharmaceutical companies. According to industry experts, the era of blockbuster drugs has approached its end, and more attention is likely to be given to specialized products that serve therapeutic niches (Aitken et al. 2009). Moreover, the scientific and economic developments demand a change in the industry's current business model and a reorganization of its R&D processes in order to secure sustainability (Garnier 2008; Munos 2009).

These trends in the pharmaceutical market place are paralleled with more stringent regulatory measures that are affecting producers, providers, and consumers alike. For instance, requirements for both market authorization and post-approval monitoring have been rising and cost-sharing instruments have been suggested to manage elevated healthcare expenditures. Besides that, demographic developments such as aging populations will have noticeable implications for public health; there will be an increased demand for drugs that treat or prevent age-related diseases such as Alzheimer's, cardiovascular conditions, or diabetes.

To be able to adequately confront these challenges, an environment is needed where novel drug introductions are valued and rewarded, and incentives are provided to invest in medicines that address critical (unmet) medical needs; where publicly- and privately funded research and development is utilized so that pharmaceutical companies no longer solely depend on sales as the primary source of financing new drug R&D; and where information

about drug safety risks is communicated in a timely manner to healthcare providers in order to guarantee wide yet safe access to medicinal products.

6.4 FUTURE RESEARCH DIRECTIONS

With the above issues in mind, we suggest in this final section several topics that we believe will be fruitful avenues for future research.

Empirical research in pharmaceutical marketing so far has paid little attention to drug price as a marketing variable. It has been generally suggested that physicians are quite unresponsive towards pharmaceutical costs. Physicians often do not know the specific price of the prescribed drug, nor do they bear the full costs; the latter has held true for many patients as well (Coscelli 2000; Kolassa 1995). However, because cost containment has become top-priority on the health care agenda due to its effect on patients' copayment and insurance coverage, the role of price in physicians' prescribing decisions may turn into a more critical factor. As a consequence, payers, particularly those confronted with financial constraints, may become more influential in the product chosen by prescribers and pharmacists. An important question is whether and how drug costs and patients' different insurance schemes will influence the prescribing behavior of physicians. Are physicians becoming more price-sensitive and how would this affect pharmaceutical demand? Recently, there has been some evidence that physicians are increasingly taking into account prices when making prescribing decisions (Laxminarajan and Li 2010; Vakratsas and Kalyanaram 2011). In that respect, it would be valuable to study the underlying mechanism by combining physician- and patient-level perspectives. Do patients communicate their budgetary constraints and explicitly request lower-priced medicines, and how do doctors respond to patients' budgetary constraints when opposing financial incentives for them are present? These issues will be of great interest for policy makers as they can have major impact on healthcare costs and public health in general, especially when they affect treatment continuation and adherence. Price effects are also managerially relevant: if physicians' price-sensitivity is increasing, pharmaceutical marketing and pricing strategies that exist today may no longer be maintained.

Another main topic that deserves more attention in future research is related to the management of drug risks. DHPCs are a key means for informing healthcare providers about new safety concerns that arise after drug approval. There is unanimous consensus that these risk communication measurements are a prerequisite to forestall (avoidable) side effects and to ensure an optimal benefit-risk balance of drugs in daily medical practice, but agreement

declines with regard to how risk information can be communicated effectively and how its impact can be assessed (Bahri 2010; Dusetzina et al. 2012). The majority of previous research (ours included) evaluates the impact of safety warnings on prescribing behavior by means of drug use volume changes; however, these outcome measures may not always be the most appropriate ones to fully assess the impact of DHPCs. Further research is needed to determine the effectiveness of DHPCs in terms of more specific measures that correspond to the safety issue in question. This requires the development and implementation of distinct process and outcome indicators.[27] The use of such specific measures can give a more complete picture of whether these risk communication activities are successful in improving the quality of clinical behavior, and eventually lead to better health outcomes (i.e., reduced occurrence of side effects). In addition, risk communication does not preclude unintended effects: some studies have reported negative spill-over effects, for example a discontinuation of the therapy in unaffected populations (for a review, see Piening et al. 2012a), which can have sizeable and costly public health consequence. Hence, when assessing the effectiveness of regulatory interventions (e.g., DHPCs) it is also important to take the costs associated with these interventions into account. Such a systematic cost-effectiveness analysis can aid regulatory decision makers in improving their risk communication strategies.

With ever more data available from drug safety reports and postmarketing studies, new tools need to be developed and implemented that allow for a structured and continuous monitoring of safety issues, and to ensure their rapid and effective detection. At the same time, for risk information to be useful, it has to be translated and communicated in such a way that it is meaningful for practice. This is a complex and challenging endeavor, not only because of the amount of data that needs to be carefully interpreted, but also because healthcare professionals differ in their perceptions and understanding of risk information (Avorn and Schneeweiss 2009; Bahri 2010). There are several important questions that should be addressed: How much and which information should be communicated to healthcare providers? Is the information always sufficiently and correctly conveyed to prompt desired changes in clinical behavior? Do physicians properly understand the message? Similarly complex issues arise in the communication of health risks to patients and the public. A better understanding of these complexities can help overcome some of the obstacles to behavior change. Finally, analyzing, interpreting, and communicating safety issues in a rigorous and effective manner calls for more interdisciplinary research that combines expertise from pharmacology, economics, statistics, psychology, and communication science.

[27] Process indicators measure changes in prescribing behavior specifically intended by the DHPC, for example the number of patients with a lower starting dose of drug X relative to all new patients using drug X. Outcome indicators measure the final output of these risk minimization activities, e.g., occurrence of adverse drug reactions.

Lastly, we propose an area for future research beyond the topic of this thesis. In view of the excitement around social media in recent years, we believe that its application in healthcare deserves further attention.

The 'social' Web has become increasingly important, transforming the way people communicate, interact, do business, and manage their lives. The growing number of online communities, blogs, forums and other consumer-initiated contributions (generally known as user generated content,[28] UGC) has not stopped at the healthcare arena. More and more patients connect with other patients, physicians, and healthcare organizations, sharing details about medical conditions or talking about drug preferences, side-effects, and dosage strategies. Understandably, pharmaceutical companies are keen to learn about how physicians and patients discuss their products' benefits and adverse effects, or compare them to competitive ones. These 'product' reviews serve companies as an important source of preference data that they can exploit for behavioral targeting strategies (Decker and Trusov 2010).

According to recent estimates, American consumers spend about one quarter of their time online on social networking sites, and more than 60 million of them engage in health-related activities on social media platforms (Kane et al. 2009; The Nielson Company 2010). For instance, sites like PatientsLikeMe (www.patientslikeme.com) or CureTogether (www.curetogether.com) provide a communication channel where patients can exchange experiences with each other. Similarly, there are several networks specifically dedicated to physicians, including Sermo (www.sermo.com) or QuantiaMD (www.quantiamd.com).

Given this enormous rise of social media usage, it is important not only to understand how and why people participate in UGC activities and disclose personal information about ailments, diagnosis and treatment histories, but also what the consequences are on health outcomes. At the same time, a pertinent question for companies and care providers is how to appropriately deal with and react to health information that is discussed in these online networks. An important issue in this context involves the online disclosure of medical information and the related privacy concerns (e.g., Goldfarb and Tucker 2012). In addition, there are also concerns about the validity of information spread through online communities. Considering that patient-user testimonials can play a non-negligible role in influencing other patients' drug use (Chan et al. 2012), these concerns are not unwarranted. Inappropriate or unsupported therapeutic claims can have negative health impacts and seriously compromise patient safety. Hence, policy makers are challenged to develop and implement guidelines for health social media sites that can both safeguard patients' privacy and protect their well-being.

[28] User generated content (UGC) is sometimes also referred to as consumer generated content.

The possibilities offered by the richness of data that is generated by users across these social media platforms have sparked great scholarly and practical interest. However, the abundance of information from these new sources of data and the complexity associated with them challenges both its processing and its analysis (Fader and Winer 2012). New methodological techniques are required that allow researchers to better mine UGC. Academic research has recently started to develop promising advanced text-mining and content analysis tools, as well as new ranking methods (e.g., Decker and Trusov 2010; Ghose et al. 2012; Netzer et al. 2012). Still, there are ample opportunities for future research to contribute to a better understanding of the effects of UGC in the healthcare arena (for some excellent examples, see Camacho 2011).

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Samenvatting (Summary in Dutch)

Het economische, maatschappelijke en politieke belang van de gezondheidszorg in het algemeen en van de farmaceutische markt in het bijzonder wordt algemeen erkend. Dit blijkt onder meer uit het deel van het bruto nationaal product dat door veel landen wordt besteed aan de gezondheidszorg. Omdat ontwikkelde economieën in toenemende mate geconfronteerd worden met financiële beperkingen, vergrijzing en technologische verandering, zijn er voor de gezondheidszorg kostenverlagende maatregelen nodig. Tegelijkertijd dient het kwaliteitsniveau van de zorg gelijk te blijven of, liever nog, te verbeteren. De farmaceutische industrie heeft een voortrekkersrol in de ontwikkeling en de marketing van nieuwe medische behandelingen. De grote hoeveelheid geld die de industrie uitgeeft aan de promotie van haar producten, maar ook de manier waarop ze marketing bedrijft zijn echter voortdurend onderhevig aan kritiek, zowel vanuit de maatschappij als van academici.

De farmaceutische markt is een complex systeem dat voortdurend in ontwikkeling is: nieuwe medicijnen worden op de markt gebracht, gezondheidsrisico's worden opnieuw beoordeeld, wettelijke richtlijnen veranderen en zorgkosten blijven stijgen. De uitdagingen die hieruit voortvloeien hebben als inspiratiebron gediend voor de vier studies die in dit proefschrift zijn opgenomen. De vier studies richten zich op drie centrale thema's, te weten:

- Hoe kunnen zelfstandige apotheken hun verkoopresultaten op peil houden in een continu veranderende zorgmarkt? (Hoofdstuk 2)
- Wat beïnvloedt de effectiviteit van de communicatie van veiligheidsrisico's voor bestaande medicijnen, zodat een juist gebruik van deze medicijnen kan worden gegarandeerd? (Hoofdstuk 3 en 4)
- Wat draagt ertoe bij dat nieuwe medicijnen snel door de markt worden geadopteerd en wanneer en hoe kunnen promotiemiddelen hierbij efficiënt worden ingezet? (Hoofdstuk 5)

Met deze studies willen we bijdragen aan de ontwikkeling van nieuwe en relevante kennis op het terrein van de gezondheidszorg en aan de bevordering van interdisciplinair onderzoek tussen marketingwetenschappers en medische academici. Hieronder vatten we de belangrijkste conclusies van de vier studies samen.

De voortdurende liberalisering van de farmaceutische markt stelt apothekers voor grote uitdagingen, met name omdat de concurrentie sterk is toegenomen. Zelfstandige apotheken worden geconfronteerd met structurele veranderingen als gevolg van toegenomen

verticale en horizontale integratie en met nieuwe regelgeving die een hoogwaardige en kosteneffectievere zorgverlening wil stimuleren. Deze ontwikkelingen dwingen zelfstandige apotheken ertoe om hun huidige ondernemingsmodel te wijzigen en commerciëler te denken. Een oplossing om de financiële druk en de concurrentie het hoofd te bieden zou kunnen liggen in het toepassen van marketingstrategieën die in de traditionele detailhandel succesvol zijn gebleken. Receptvrije medicijnen vormen in dit verband een steeds belangrijker segment voor zelfstandige apotheken, omdat hiermee mogelijk aanvullende inkomsten kunnen worden gegenereerd.

In Hoofdstuk 2 onderzoeken we welke product-, winkel-, klant- en concurrentiekenmerken de verkoop van receptvrije geneesmiddelen, en daarmee de totale verkoopresultaten van de apotheek, beïnvloeden. We trekken twee belangrijke conclusies: ten eerste vinden we dat het assortiment en verkooppromoties twee cruciale factoren zijn die verkoopresultaten van de apotheek beïnvloeden. Ten tweede laten onze resultaten zien dat factoren die belangrijk zijn voor traditionele detailhandel (zoals locatie en winkelkenmerken) minder relevant zijn voor zelfstandige apotheken. Deze bevindingen zijn belangrijk voor het management van zelfstandige apotheken omdat zij hiermee meer inzicht krijgen in de voordelen van een geconcentreerde, strategische marktbenadering zoals die door de detailhandel al veel langer wordt toegepast. In de praktijk zien we dat juist dit aspect onder apothekers vaak nog weinig ontwikkeld is: zij zien zichzelf in de eerste plaats vaak als zorgverleners en pas in de tweede plaats als detaillisten.

Ondanks strenge toelatingscriteria zijn niet alle gebruiksrisico's van een nieuw geneesmiddel altijd volledig duidelijk op het moment dat het op de markt wordt geïntroduceerd. Bepaalde veiligheidsproblemen worden pas zichtbaar wanneer het nieuwe medicijn langere tijd wordt voorgeschreven aan een bredere populatie. Recentelijk zijn er dan ook verscheidene medicijnen vanwege veiligheidsproblemen van de markt gehaald en zijn er zorgen over de veiligheid van andere receptgeneesmiddelen. Dit heeft ertoe geleid dat er meer aandacht is voor de manier waarop veiligheidsrisico's van geneesmiddelen gecommuniceerd worden naar zorgverleners. Uit het beperkte aantal studies waarin dit onderzocht wordt, blijkt dat deze risicocommunicatie niet altijd effectief is en dat dit in veel gevallen dus ook niet leidt tot de gewenste veranderingen in voorschrijfgedrag.

In de Hoofdstukken 3 en 4 proberen we beter inzicht te verkrijgen in de effectiviteit van risicocommunicatie voor receptgeneesmiddelen. De risicocommunicaties die we in deze hoofdstukken onderzoeken zijn zogenaamde "Direct Healthcare Professional Communications" (DHPCs). Wanneer er een veiligheidsprobleem geconstateerd wordt bij het gebruik van een geneesmiddel is de producent verplicht een brief te sturen naar

de zorgverleners die dit middel mogen voorschrijven. In deze brief wordt het probleem uiteengezet en wordt aangegeven hoe het voorschrijfgedrag aangepast zou moeten worden.

In Hoofdstuk 3 onderzoeken we het effect van de DHPCs op het voorschrijfgedrag van artsen voor een breed scala aan producten, gedurende een langere periode. Uit onze analyses komt naar voren dat op de korte termijn bij ongeveer de helft van de geneesmiddelen waarvoor een DHPC is uitgeschreven het aantal voorschriften afneemt. Op de langere termijn valt bij slechts een derde van de medicijnen met een DHPC een verandering in gebruik waar te nemen. Onze resultaten ondersteunen het beeld dat de effectiviteit van risicocommunicaties behoorlijk varieert. Onze resultaten tonen echter ook aan dat een DHPC in sommige gevallen kan leiden tot een substantiële afname in het aantal voorschriften voor het betreffende geneesmiddel.

In Hoofdstuk 4 onderzoeken we welke kenmerken van het geneesmiddel en van de DHPC het effect van de DHPC beïnvloeden. We vinden dat het voorschrijfgedrag beïnvloed wordt door de specialistische status van het medicijn waarvoor de DHPC is uitgeschreven, de ernst van het veiligheidsrisico, het al dan niet gebruiken van een standaardbrief voor de DHPC en door de aan- of afwezigheid van een dalende trend in het aantal voorschriften voordat de DHPC werd uitgegeven. Regelgevende instanties en farmaceutische bedrijven kunnen onze resultaten gebruiken bij het verder optimaliseren van de communicatie van veiligheidsrisico's aan zorgverleners en bij het evalueren van risicobeperkende maatregelen.

Voor farmaceutische bedrijven is het van belang om inzicht te krijgen in de factoren die de adoptie en diffusie van nieuwe medicijnen beïnvloeden. Hierdoor kunnen de hoge ontwikkelkosten immers sneller worden terugverdiend. Het succes van (ver)nieuw(d)e medicijnen hangt van vele factoren af, maar belangrijke determinanten zijn de snelheid waarmee het product wordt geadopteerd en het aantal voorschrijvers.

In Hoofdstuk 5 onderzoeken we of de fase in het adoptieproces, de marketing-inspanningen van de farmaceutische industrie en arts-specifieke kenmerken van invloed zijn op het voorschrijfgedrag van artsen. We nemen een bekend model uit de diffusieliteratuur als basis en gebruiken dit om het adoptiegedrag van individuele artsen te bestuderen. Onze resultaten tonen aan dat de neiging om het nieuwe product voor te schrijven verschilt tussen artsen. We vinden ook dat artsen verschillen in de manier waarop het voorschrijfgedrag beïnvloed wordt door artsenbezoekers. We constateren dat deze verschillen onder meer afhangen van arts-specifieke kenmerken en de fase van het adoptieproces waarin de arts zich bevindt. We laten zien dat managers met behulp van onze uitkomsten beter kunnen inschatten wanneer welke arts het meest gevoelig is voor marketingactiviteiten en dat goed gebruik hiervan zich ook vertaalt naar hogere omzetten voor het betreffende geneesmiddel. Met

behulp van deze kennis kunnen farmaceutische-marketingmanagers effectievere strategieën ontwikkelen voor het gericht benaderen van artsen uit hun doelgroep.

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John F. Kennedy

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