Innovation, pricing and regulatory policies in the German pharmaceutical market

Zur Erlangung des akademischen Grades eines
Doktors der Wirtschaftswissenschaften
(Dr. rer. pol.)
von der Fakultät für
Wirtschaftswissenschaften
des Karlsruher Institut für Technologie (KIT)
genehmigte
DISSERTATION
von Dipl.-Vw. Christoph de Millas

Tag der mündlichen Prüfung: 30.05.2016
Referent: Prof. Dr. Kay Mitusch
Korreferent: Prof. Dr. Hagen Lindstädt

Widmung

Meiner Familie und meinen Unterstützern

Danksagung

Mein erster Dank gilt meinem Doktorvater Herrn Prof. Dr. Kay Mitusch, der mir bei der Erarbeitung der vorliegenden Dissertation stets hilfreich zur Seite gestanden hat. Ohne seine konstruktiven Anmerkungen, seine kritischen Nachfragen, seine Zeit und sein stets offenes Ohr wäre diese Arbeit nicht gelungen. Herzlichen Dank für die gute Betreuung.

Mein zweiter Dank gilt Herrn Prof. Dr. Hagen Lindstädt für seine Bereitschaft sich als Gutachter meiner Arbeit anzunehmen.

Bei Herrn Prof. Dr. Bertram Häussler und Herrn Dr. Martin Albrecht möchte ich mich für die Möglichkeit und Unterstützung bedanken, im IGES Institut meine Doktorarbeit schreiben zu können. Ebenso möchte ich meiner Vorgesetzen Frau Dr. Ariane Höer danken, dass sie mir den Rücken frei gehalten hat, um Zeit für die Doktorarbeit zu finden. Die Tätigkeit im IGES Institut half mir das grundlegende Verständnis für den deutschen Arzneimittelmarkt anzueignen und war eine Quelle der Inspiration für die Themen dieser Arbeit Ein besondere Dank gilt dabei für die Erlaubnis, die im IGES Institut zur Verfügung stehenden Datensätze zu nutzen. Die Arbeit wäre in dieser Form sonst nicht möglich gewesen.

Bei meinen Kollegen im IGES Institut möchte ich mich für die Unterstützung bedanken. Das außergewöhnlich gute kollegiale Klima und die immer vorhandene Hilfsbereitschaft bei der Beantwortung von Fragen habe ich sehr zu schätzen gelernt. Zuvorderst gilt mein Dank meinem Doktorandenkollegen Herrn Dr. Robert Haustein für die fachliche und freundschaftliche Zusammenarbeit bei der Erstellung der gemeinsamen Paper und der Übernahme meiner betrieblichen Aufgaben während meiner dreimonatigen Auszeit, die ihn in dunkle Höhlen der Datenverarbeitung führte. Herrn Alexander Piel danke ich für die Unterstützung bei der EDV-gestützten Aufbereitung der Daten.

Auf privater Ebene möchte ich meinen Freunden und meinen Eltern für ihre Geduld danken, da diese Arbeit doch deutlich mehr Zeit als geplant veranschlagte. Meiner Nichte Inari Friedmann, Lucile Bourgery und Marcel Kummerant danke ich für grammatikalische Korrekturen.

Content

Figures

Tables

I. Abstract

The three major cost factors in the German Statutory Health Insurance (SHI) system are inpatient care, outpatient care and prescription drugs. Competition is restricted in inpatient and outpatient care in order to ensure an economic basis for providers and a comprehensive supply of care. Pharmaceutical companies do not face this kind of market protection. They bear the operational risk themselves, market access is only limited by safety regulations, and prices are set freely in most cases. National legislators want to leverage on this power of the market, but at the same time public opinion demands a strong control over the provision of care.

The thesis analyzes - both theoretically and empirically - the impact of national regulative instruments on the German pharmaceutical market. The discussed regulative instruments are reference pricing, co-payments, lead compounds, rebate contracts and the so called “early benefit evaluation”. The thesis consist of four independent essays.

The first paper of the thesis analyses the influence of the regulative instruments (with the exception of the early benefit evaluation) from the perspective of the SHI physicians. In detail, the probability is estimated that a physician will dispense to a patient a different drug than the last time. The analysis uses routine data of a large German sickness fund that contains prescription data on patient level for three major indication areas. The results show the significance of both the patient’s and the physician’s habits as well as drug-related characteristics. These results give evidence for existing persistence in drug choices. In regard to the impacts of regulatory instruments, the strongest effect is found for rebate contracts, followed by reference pricing and exemption from patient related co-payments. Correspondingly, the probability for a switch to an active ingredient is lower for drugs under patent protection. It indicates the reluctance of physicians to

prescribe new drugs. This might discourage innovations that are only slightly superior to the existing therapy standards.

As the strongest effect was found for rebate contracts, the second paper of the thesis elaborates a theoretical approach to explore the working of rebate contracts. These are contracts between sickness funds and generic drug producers that guarantee market exclusivity. Two different types of rebate contracts are modeled: contracts considering only one specific active ingredient (API contracts) and contracts including the whole product portfolio of a producer (portfolio contracts). There are two generic producers, but only one can offer a portfolio contract; this latter company stands for a large and well-known pharmaceutical firm. There are also two types of sickness funds representing two different groups of insurants. For one group, products offered by both producers are seen as homogenous while the other group has a preferred producer, which is the one that can also offer a portfolio contract. It is found that the preferred producer has an advantage in three out of four possible parametric scenarios. It can outrival the other firm due to its monopolistic power and its portfolio. But sickness funds can still save money as the threat of rebate competition is not sufficient to prevent market entry. As long as mismatch costs and access costs are low and portfolio contracts are not allowed, the forces of competition are active in protecting consumers, even though the market result looks like a monopoly.

The third paper is a descriptive essay about the particular economics of research and development in the pharmaceutical industry. It discusses the economic situation of the pharmaceutical industry in the light of diverging political demands. Industrial politics is in favor of the industry. Health politics sees it as an important health care input, but also has concerns about the ratio of cost to effectiveness. This ratio is generally regarded as being too low. The problems are seen in the research process of a drug. There are indications for high internal inefficiencies, but regulatory demands have also a negative effect on the output. Furthermore, the short-term view of the capital market may not reward long range research projects sufficiently. Pharmaco-economic evaluations are seen as a

potential solution. They try to objectify the benefit of a drug and to define acceptable cost-effectiveness levels.

The last paper discusses theoretically the introduction of such a pharmaco-economic approach in Germany: the so called early benefit evaluation. After market approval, the manufacturer has to hand in a dossier demonstrating the additional benefit of its product compared to an established therapy. Based on the granted benefit, the sickness funds and the manufacturer negotiate the reimbursement price. The starting point of the model is the investment decision of a pharmaceutical firm. The objective benefit of a drug is a random output. Additionally, the company can induce a subjective benefit to the patient. The reform is described as a change in the information regime. Before the reform, the physicians cannot observe the true benefit of a drug and they develop expectations towards it. After the reform, the early benefit evaluation reveals the objective benefit and limits the reimbursement to this value (i.e. it ignores any subjective benefits). In an extension of the model, the manufacturer can either invest in a step (low variance) or a leap (high variance) innovation. Calibrated by data from early benefit evaluations for the first three years (2011 to 2014), the model indicates that the reform did not increase the incentives for leap investments, as it was intended. In conclusion, the reform might encourage future investments through benefit orientated pricing, but the probabilities for real breakthroughs might be diminished.

II. Introduction

When it comes to debates about the German health market, the main topic of interest is the German Statutory Health Insurance (SHI, *Gesetzliche Krankenversicherung* (GKV)) system as it insures over 85 % of the German citizens.[1] These insurants receive both outpatient (ambulant care) and inpatient (hospital care) services in various forms.

Consequently, the pharmaceutical market of the SHI system is the largest in Germany. It accounts for about 72 % of all expenditures for pharmaceuticals (excluding hospitals)[2]. The market is also an important cost factor within the SHI system. In 2013, the expenditures for pharmaceuticals amounted to 30.1 billion euro and were the third largest cost pool in the SHI system, behind spending for hospitals and physicians.[3] The sickness funds only spent more for medical services in ambulant care (31.4 billion euro in 2013) and for hospital treatments (64.2 billion euro in 2013).[4]

Furthermore, pharmaceutical expenditures showed a strong increase since the beginning of the century. From 2000 to 2010, the annual growth rate for pharmaceutical expenditures was 4.5 % compared to 2.1 % in outpatient care and 2.8 % in inpatient care (Figure 1). In the years since 2011, a significantly slower development can be observed because of reform acts. The expenditures for pharmaceuticals in 2013 were lower than in 2010 (an annual growth rate of -0.1 %), whereas outpatient care (3.4 %) and inpatient care (5.1 %) showed stronger growth.

---

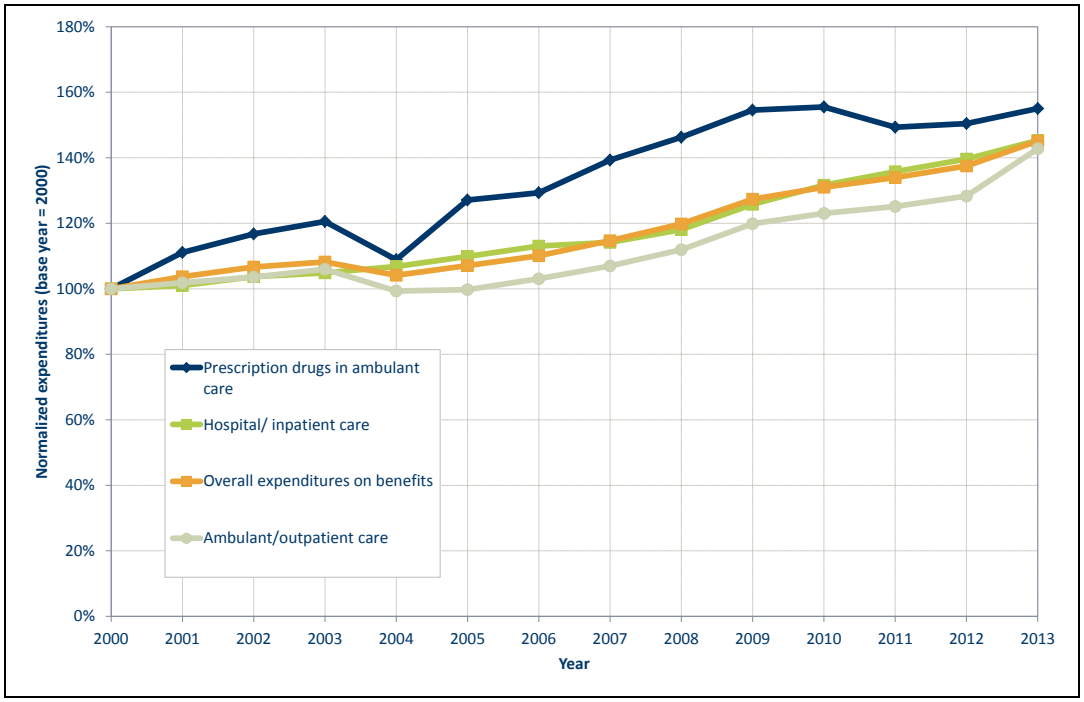
1 See Bundesministerium für Gesundheit (2014b) and Statistisches Bundesamt (2014a)

2 See Statistisches Bundesamt (2014b)

3 See Bundesministerium für Gesundheit (2014a)

4 See ibid.

Figure 1: Development of expenditures in the SHI system (index, year 2000 = 100), 2000-2013



Source: Bundesministerium für Gesundheit (2014a)

Competition is restricted in inpatient and outpatient care in order to ensure an economic basis for providers and a comprehensive supply of care. Pharmaceutical companies do not face this kind of market protection. They bear the operational risk themselves, market access is only limited by safety regulations, and prices are set freely in most cases. National legislators want to leverage on this power of the market, but at the same time public opinion demands a strong control over the provision of care.

Strong regulations often lead to a reduction of expenditures for the SHI system. Normally this also means a decline in sales for the pharmaceutical industry. As a consequence it diminishes the financial capacities for future research. Hence, short term savings for SHI system might lead to social cost in the long run. The legislator is aware of this problem. Therefore, regulation is not limited to simple price cuts or exclusions from reimbursement but it tries to give motivations in a way, that the economic incentives for research remains active. Substantial innovations should be rewarded whereas questionable ones should not.

Thereby, a regulative instrument does not necessarily target directly the pharmaceutical industry but also other stakeholders involved in the process of supply and demand with prescription drugs such as sickness funds, physicians, pharmacies and patients.

The aim of this thesis is to analyze the effects of the most important regulative instruments within the SHI system between 2004 and 2011 in regard to pharmaceuticals. The papers presented in the next chapters display the effects of the instruments on the prescription behavior of physicians, the strategic behavior of pharmaceutical companies and sickness funds in negotiations as well as development decisions for new products as a reaction of pharmaceutical companies to benefit evaluations. It is of special interest whether the reforms achieved the expected (or feared) outcomes.

This introduction of the thesis (Chapter II) gives a description of the relevant regulative instruments that will be discussed in the different papers. Additionally, an overview is given of the various datasets, statistic and mathematical software tools used in the papers.

The physician is probably the most important stakeholder in a reform because he decides on the active ingredient that will be dispensed. The paper in Chapter III examines if regulative changes increase the probability for a change in the dispensed drug.[5] The legislator wants to increase incentives for the prescription of cheaper and/or therapeutically preferred active ingredients through the introduction of the following instruments: reference pricing, exemptions from patient related co-payments, lead compound rule, and rebate contracts. Using a patient-level panel dataset from a large SHI sickness fund covering three major therapeutic groups, the probability for a switch of the drug dispensed is estimated as a function of physician-, patient- and drug-related characteristics and habits.

[5] This part of the thesis is a joint work with Robert Haustein. Both authors contributed in equal parts to the development of the model and its empirical evaluation. Lead author of the manuscript was Robert Haustein.

The second paper of the thesis (Chapter IV)[6] analyses the concept of two different kinds of direct rebate contracts between sickness funds and pharmaceutical companies for generic drugs on a theoretical basis. More explicitly, the goal of the analysis is to show whether rebate contracts are a way to save drug expenses or if they lead to oligopolistic drug supply structures, followed by a long-term increase of drug expenses. For that, the provided model examines the strategic interaction between two types of generic producers and two kinds of consumers/sickness funds. The considered generic producers differ only in the range of their product portfolio, as one of them provides a larger variety of active ingredients while the other only offers one active ingredient. The demand side is represented by consumers/sickness funds of a first type, for whom the two offered generic products are homogenous, and a second type holding a preference for a specific generic producer. Considering the differences in the consumer preferences using a Hotelling approach, the possibilities of Nash equilibria in pure strategies for the resulting strategic interactions in the negotiation process of rebate contracts between the firms and consumers/sickness funds are investigated. Thereby two types of rebate contracts are analyzed: single active pharmaceutical ingredient contracts and portfolio rebate contracts.

The essay in Chapter V elaborates on the economy and current development of research and development (R&D) in the pharmaceutical industry. The insights of the essay lead over to the third paper (Chapter VI) that analyzes the latest fundamental reform in the German pharmaceutical market. The AMNOG legislation (Act on the Reform of the Market for Medicinal Products)[7] introduced in 2011 the so called "early benefit evaluation". The legislator hopes as a result to establish benefit related prices, to set an incentive for significant innovations, and ultimately to save cost. The market model in Chapter VI focuses on the aspect of

---

[6] This part of the thesis is a joint work with Robert Haustein. Both authors contributed in equal parts to the development of the model and its elaboration. Lead author of the manuscript was Christoph de Millas.

[7] Officially *Gesetz zur Neuordnung des Arzneimittelmarktes* or *Arzneimittelmarktneuordnungsgesetz.* The abbreviation AMNOG has established itself as the term for the whole evaluation process.

innovation. Under the AMNOG, the producer has to hand in a dossier demonstrating the additional benefit of its product compared to an appropriate comparator after market approval of a new molecule entity. Based on the benefit accepted by the responsible authority, the sickness funds and the manufacturer negotiate the reimbursement price. The market model describes the reform as a change in the information regime. Starting point of the model is the investment decision of a pharmaceutical firm. The random output is the objectively verifiable benefit of a drug. Additionally, the company can induce a subjective benefit. Before AMNOG, the physicians cannot observe the true objectively verifiable benefit of a drug and they develop expectations towards it. As a first goal, the early benefit evaluation reveals the objective benefit of the drug and limits (or increases) the reimbursement to its value. Hence, there is a tendency of lower average profits through the reform. As a second goal, the evaluation wants to shift the development decisions of the firms. In the model, the manufacturer can either invest in a step (low variance) or a leap (high variance) innovation. Supported by information from early benefit evaluations of the first three years (2011 to 2014), the model indicates no higher incentive for leap investments. As a conclusion, the reform might encourage future investments through benefit-orientated pricing but the probability of real breakthroughs might be diminished.

II.1 Regulation and control of the research process in the German health care system

There exist various ways of influencing the investment decision of pharmaceutical firms; the effects of patents and market authorization will be presented in Chapter V. In the following, the focus is on regulative instruments of the German statutory health insurance system, which are presented, analyzed and discussed in the upcoming Chapters III, IV and VI (these instruments are: reference pricing, co-payments, lead compounds, rebate contracts and the early benefit evaluation).

II.1.1 The system of prescribing drugs in ambulant care in the German SHI system

Since its introduction in 1883, the German statutory health insurance system (SHI, *Gesetzliche Krankenversicherung* (GKV)) follows the Bismarck model.[8] Insurance to the citizens is provided by non-profit sickness funds and is jointly financed by employees and employers through payroll deductions.[9] Services are provided under the "principle of benefits" (*Sachleistungsprinzip*). It means that there is no financial transaction between patients and the providers of health services, with the exception of small co-payments. Physicians and hospitals receive reimbursement directly or indirectly (through regional associations) from the sickness funds. The payments are based on regional and national agreements. The principle of benefit also applies for the ambulant pharmaceutical market.

The SHI system covers over 85 % of the German population.[10] The insurance is compulsory for all employees and pensioners up to a certain annual gross income (€54,900 in 2015).[11] The others receive comprehensive coverage through a private health insurance (PHI).[12] The PHI system as a full coverage insurance is open to employees and pensioners above the income limit, civil servants (in addition to special allowance (*Beihilfe*) from the state) and self-employed persons. In opposite to the SHI system, services are provided under the "cost reimbursement principle" (*Kostenerstattungsprinzip*), but fees are also regulated on a national (physicians) and regional (hospitals) level.

The regulations for the supply of pharmaceuticals are basically the same in the SHI and PHI system. The physicians are responsible for the prescription of

---

8 See Bump (2010), p. 14

9 See Wallace (2013), p. 84

10 See Bundesministerium für Gesundheit (2014b) and Statistisches Bundesamt (2014a)

11 See Bundesregierung (2014)

12 Since 2009 health insurance is compulsory in Germany

drugs.[13] The patient submits these prescriptions to pharmacies in order to receive the product. The prescription is nearly fully reimbursed in the SHI system by the sickness funds.[14] The patient only has to pay a small co-payment. In the PHI system the co-payments depend on the individual contract. In a few cases under the SHI system, the patient has to pay additionally the difference between the maximum reimbursement price and the list price (see section II.1.2). The pharmacists receive payments based on the exact documentation of the dispensed drugs. The pharmacies are supplied with products by wholesalers or directly by pharmaceutical producers.

II.1.2 Important reforms in the German SHI system since 2002

The different papers in this work analyze the implementation or modification of five regulative instruments of the German pharmaceutical market: reference pricing (Chapter III), co-payments (Chapter III), lead compounds (Chapter III), rebate contracts (Chapter III and IV) and the early benefit evaluation (Chapter VI). In the following, the different instruments shall be presented in the context of the legal reform, in which they were introduced or significantly modified.[15]

Law on Limiting Pharmaceutical Expenditure - *Arzneimittelausgaben-Begrenzungsgesetz* (AABG) from 2002

Aut-idem[16]

The aut-idem rule mandates pharmacies to exchange expensive with cheaper products of the same active ingredient if they are available in the same strength

---

[13] See § 73 (2) SGB V (Social Code Book 5)

[14] See § 61 SGB V

[15] . It should be noted that it does not include all direct and indirect instruments targeting the pharmaceutical market. See Busse & Blümel (2014) for a more comprehensive overview.

[16] See § 129 (1) SGB V

and package size. The rule was implemented in 1989.[17] When the physician names only the international nonproprietary name (INN) of the active ingredients on the prescription, the pharmacist must choose between one of the three drugs with the lowest price. If the physician writes a specific product name, the pharmacist can also choose the named product instead of the three cheapest. Before 2002, the physician had explicitly cross on the prescription that he allows aut-idem. Since then, it is the other way round. This small change had a significant impact. Before the reform, the physicians would not allow aut-idem because of inadvertence. Now it is a distinctive decision. In regard to original drugs, this accelerates the degeneration phase of them after patent expiry because physicians might write down the name of the original product out of habit. With the change in 2002, generics gain market share more quickly and the originator has a higher pressure to launch a new product.

SHI Modernization Act - *GKV-Modernisierungsgesetz* (GMG) from 2004

Reference price system[18]

While the aut-idem rule influences the competition between products of the same active ingredient, the reference pricing system can also intensify competition between different ones. Reference pricing has primarily a strong influence on pricing of prescription drugs. Together with the aut-idem rule, it was implemented in 1989, and Germany was the first country which such a regulation. It sets a uniform reimbursement limit – the reference price (RP) – for one or several active ingredients (the limit is differentiated by package size and strength). It affects all producers providing drugs containing the active ingredient. Patients are also affected. When the price of a product exceeds the reimbursement level, patients must pay the difference between the RP and the retail price.[19] The German system distinguishes three types of reference price groups. The first group only includes

---

17 See *Gesundheits-Reformgesetz* (GRG) passed in 1988

18 See § 35 SGB V

19 See Giuliani *et al.* (1998), p. 74

products of the same active ingredient (original and generic). The second group includes pharmacological-therapeutically and chemically comparable active ingredients. The third group encompasses active ingredients that are therapeutically comparable (especially combinations). In 1996, patent drugs (with market approval after December 31st 1995) were excluded from the reference price system. Since 2004, patent protected drugs can be incorporated again into reference price groups of the second or third type. The reference price groups consist either of various patent protected drugs (at least three) or of a mixture of patented originals, off-patent original drugs and their generic versions.[20] These mixed groups are also called "jumbo-groups". The groups are defined by the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA). The G-BA is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany.[21] The level of the specific reference prices are set by the Association of Sickness Funds (*GKV-Spitzenverband)* in agreement with the Federal Ministry of Health (*Bundesministerium für Gesundheit*, BMG) and can be revised annually. The reference price is based on the price level of a defined "standard package" characterized by package size, strength and active ingredient. Obviously, the standard package in a "jumbo-group" is from a generic drug. The original prices of patent drugs are therefore normally above their reference price in a jumbo-group. A jumbo-group is de facto a prevention of further market entry for new drugs that are not innovative (in the opinion of the G-BA). Such new drugs with pharmacological-therapeutically and chemically comparable counterparts are often called "me-too" drugs. Most patients will not be willing to pay the difference between retail price of the me-too and reference price. Additionally, a price on the level of the reference would make it nearly impossible to refinance research costs, especially as other countries often refer to German prices when

[20] See Stargardt *et al.* (2005) for a detailed overview

[21] G-BA (2014)

they define their own reimbursement prices.[22] A new me-too drug can only avoid the reference price system if it can prove that it is significantly better regarding efficacy and side effects than its pharmacological-therapeutically and chemically counterparts. It is very uncommon that a me-too drug can demonstrate that.[23]

Economic Optimization of Pharmaceutical Care Act - *Gesetz zur Verbesserung der Wirtschaftlichkeit in der Arzneimittelversorgung* (AVWG) from 2006

Co-payments[24]

Patients not only face exceptional additional payments (*Aufzahlung)*, as described in the last paragraph, but also regular co-payments (*Zuzahlung).* Starting with one Deutsch Mark in 1977[25], the last change was in 2004 with the SHI Modernization Act (GMG). Patients have to pay a prescription related co-payment of 10 % of the retail price, but at least five euro and at most ten euro. Drugs priced lower than five euro have to be paid completely by the patient. Consequently, the effect of co-payments on the price sensitivity of patients is relatively weak, especially for patent prescription drugs. However, co-payments are regarded as a mode of limiting the moral hazard problem related with the consumption of drugs.[26] The co-payments are also a considerable source of funding amounting to 2,013 million euro in 2013.[27]

There exist exemptions from the co-payment rule. Patients suffering from a chronic disease, minors and patients with a low income are, or can be, excluded completely or partially from co-payments.

---

22 See Tuomi *et al.* (2013), p. 20 for an overview

23 The case of escitalopram is one recent exception. See Anonym (2011)

24 § 61 SGB V

25 See *Krankenversicherungs-Kostendämpfungsgesetz* (KVKG) passed 1977

26 See Thomson & Mossialos (2004), p. 227

27 See Bundesministerium für Gesundheit (2014a)

In 2006, a significant change was made to the co-payment regime which had an influence on price competition. Since the reform, the *GKV-Spitzenverband* can exempt drugs in certain reference price groups from co-payments**,** when their retail price is 30 % below the reference price. This makes the market entry for patent drugs that will be integrated into a reference price group even less profitable and it increases price sensitivity.

Lead compound[28]

Although physicians have therapeutic freedom about the chosen medication, various regulative instruments try to direct their decisions. Most physician related regulations are established on the regional or individual level. The *GKV-Spitzenverband* and the National Association of Statutory Health Insurance Physicians (*Kassenärztliche Bundesvereinigung*, KBV) decide only on a framework agreement. It includes the agreed growth rate for outpatient drug expenditures for the following year as well as supply and efficiency goals for the SHI system. Based on this, the individual quarterly budgets and annual goals are defined on the regional level. The individual quarterly drug budget depends on their number of patients, the region, specialization and age of the patients. When a physician exceeds his budget and does not reach his efficiency goals, he might be liable for the additional costs and has to refund them to the sickness funds.

In 2007, lead compounds for selected therapeutic areas were implemented as an efficiency goal.[29] Regional drug agreements can include quotas determining that a certain percentage of dispended drugs in the specific indication area should belong to the chosen active ingredient (lead compound). For example, the framework agreement of 2015 states that simvastatin and pravastatin should account for 82 % of all dispensed HMG CoA reductase inhibitors.[30] This system can also influence the prescription decision when all products are already under

---

[28] See § 84 (1) SGB V

[29] See KBV (2007), p. A72

[30] See KBV (2014), p. 7

the reference price but some are still cheaper. Furthermore, it also encourages the switch between therapeutic alternatives belonging to different chemical subgroups that cannot be included into the same reference price group. Again, it gives a signal to the pharmaceutical industry that further market entry in the specific field is unprofitable.

Act to Strengthen Competition in the SHI System - *GKV-Wettbewerbsstärkungsgesetz* (GKV-WSG) from 2007

Rebate contracts[31]

Introduced in 2003,[32] rebate contracts are individual agreements between producers and sickness funds on additional discounts for specific products. They usually cover all products with a specific active ingredient from the same producer but more specific contracts are also available. Contracts over the whole product portfolio of a producer were originally possible. Since 2009, there were initiatives to repress them. They are still not forbidden technically but legal requirements introduced in 2012 make them impossible.[33] Rebate contracts were not common until 2007, because sickness funds could not force pharmacists to dispense the discounted product. The GKV-WSG achieved that through changes to the aut-idem rule.[34] Since then, pharmacists are obliged to dispense the drugs which are part of the rebate contract unless the physician has not ruled out substitution.[35] Following the conclusion of a rebate contract, sickness funds can exempt the rebated drugs from half or all co-payments for the patients.[36]

Generic drugs are the primary target of rebate contracts. In combination with the aut-idem rule, the contracts are also a tool to ensure fast market penetration of

---

31 See § 130a (8) SGB V

32 See *Beitragssatzsicherungsgesetz* (BSSichG) passed 2003

33 See Bundestagsdrucksache 17/10156 (p. 95)

34 The legal change is often called the „arming“ of rebate contracts.

35 Recall aut-idem rule on page 19

36 See § 31 (3) SGB V

generics after patent expiry. Contracts often start directly with the market launch of the generics.

But rebate contracts have also become more interesting for patented drugs. The conditions in rebate contracts are confidential. Hence, it allows price reductions without changing official list prices. At the moment, research-based companies mainly use the agreements to regain market share from re-import firms.[37] More sophisticated contracts ("add value contracts") are also possible and can be used as a marketing tool.[38] Pharmaceutical companies can offer additional services with treatments; they can share the risk when the treatment fails; they can take over costs when prescriptions exceed a defined limit etc. [39] Since 2011, pharmaceutical companies are also allowed to be partners in integrated care programs.[40]

Rebate contracts could also accelerate the diffusion of innovative drugs in the SHI market. As already described, physicians in the outpatient sector have an individual quarterly drug budget. Prescriptions under a rebate contract can be excluded from the budget making the physicians more willing to prescribe the new drug.

Act on the Reform of the Market for Medicinal Products - *Arzneimittelmarktneuordnungsgesetz (*AMNOG*)* from 2011

Early benefit evaluation[41]

Germany is one of the few industrial countries with direct market access after approval and free pricing. This has led to a debate whether new drugs are worth their price and whether too many drugs of questionable value enter the German market.

---

37 See Häussler & de Millas (2014), p. 38

38 See Janning (2010)

39 See vfa (2011)

40 See Landschek (2011)

41 See § 35a SGB V

With the GKV-WSG in 2007, there was a first attempt at benefit related prices. On behalf of the G-BA, the Institute for Quality and Economic Efficiency (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG) would had conducted a cost-effectiveness-analysis for selected drugs. The price ceilings would had been either negotiated on a voluntary base between the pharmaceutical companies and the *GKV-Spitzenverband* or would had been set based on the result of the analysis. However, the regulation was replaced in 2011 before the first cost-effectiveness-analysis was ever completed.

On January 1st 2011, the so called early benefit evaluation (*frühe Nutzenbewertung*, fNB*)* was introduced. Nearly every new molecular entity (NME) launched in the German drug market has to go through it. The only exception is for NMEs with expected revenue in the outpatient sector of less than one million euro per year. Responsible for the evaluation is the G-BA. When a NME enters the market, the G-BA assesses within six months (three months for evaluation and three months for the hearing) whether a claimed additional benefit in relation to an appropriate comparator (*zweckmäßige Vergleichstherapie*, ZVT) is proven. Instead of a cost-effectiveness-analysis, only an effectiveness-analysis is conducted. The company submits a dossier to the G-BA based on the authorization documents and premised on all studies carried out on the NME.[42] The producer must prove the additional benefit of the pharmaceutical in comparison to at least one ZVT (the definition of subgroups with different ZVTs is possible) set forth by the G-BA. The evaluation of the dossier through IQWiG and G-BA is based on the international criteria for evidenced based medicine. The extent of the additional benefit is not reported as a specific value but as one of six categories about the benefit[43] and one of four categories about the certainty of

---

[42] See Schlette & Hess (2013), p. 4

[43] (1) major: sustained and large improvement; (2) significant: considerable improvement; (3) minor: moderate and not merely slight improvement; (4) not quantifiable: there is an additional benefit, which is not quantifiable however, because the scientific base data do not permit this; (5) no additional benefit proven; (6) less than the benefit of the ZVT

results.[44] Based on these results and price information from fifteen European countries, the pharmaceutical manufacturer and the *GKV-Spitzenverband* negotiate the reimbursement price.[45] The negotiation process can take up to six months, which means a total of one year till the negotiated price is settled. Within that time the drug is reimbursable under its original price. When the parties cannot find an agreement, an arbitration body decides within three months.[46] The decision of the body applies retroactively to the end of the negotiation period. Until March 2013, the reimbursement price was a discount on the list price, since then the reimbursement price is the official list price. This will most likely have a direct effect on other European countries that refer to the German prices.

Systems like the early benefit evaluation are often called a fourth hurdle of market authorization (besides quality, safety and efficacy). In Germany it is not a real fourth hurdle because it does not deny market entry if the product provides no benefit. A form of value based pricing is established in many countries[47] and even though there are international standards about the evaluation of pharmaceuticals, there is sufficient room for interpretation for agencies to come to diverging results based on the same information. There can be for example differences regarding extent (e.g. efficacy, cost-effectiveness, budget impact), perspective (e.g. patients, public payer, society), analytical method (e.g. cost minimization or relative to effectiveness/utility/benefit) and comparator (e.g. existing practice, cheapest, medical/non-medical).[48] The timing also plays an important role. Many drugs can only show their full benefit in the long run and most of the time there is no consensus for causalities between patient relevant endpoints and surrogate parameters. In Germany, the legislator tries to consider that. After at least one

---

44 (1) proof; (2) indication; (3) hint; (4) not stated

45 See § 130b SGB V

46 See Cassel & Ulrich (2014), p. 3

47 See cross-national overviews by Bouvy & Vogler (2013), Kanavos *et al.* (2010) and Paris & Belloni (2013)

48 See Paris & Belloni (2013), p. 20-36

year, the manufacturer or the G-BA can demand a new evaluation. Sometimes, the G-BA directly declares an early benefit evaluation temporary and the manufacturer must hand in a new dossier after some time (usually two to three years). The cost-effectiveness-analysis introduced in 2007 is also still possible. [49] Within one year after the early benefit evaluation, the manufacturer or the *GKV-Spitzenverband* can ask for a comprehensive cost-effectiveness-analysis by the IQWiG (by the end of 2015 none has been demanded).

In contrast to the other regulative instruments, the early benefit evaluation should give a strong incentive for innovation because a larger benefit means higher prices. Chapter VI will outline that the situation is a bit more complex. Companies will most likely focus on indications where it is easier (and cheaper) to demonstrate an additional benefit. Orphan drugs and areas of high medical need could be such indications.

II.2 Datasets and econometric software used in the thesis

The empirical analyses in Chapter III are based on three different datasets.

The first dataset, provided by the German market research company INSIGHT Health, contains approximately 99 % of the drug prescriptions in the German SHI market, covering the time span from January 2004 to December 2007 on a monthly basis. The data includes information on sales volume and the amount of dispensed Defined Daily Doses (DDD) for each manifestation in terms of strength, package size and dosage form, of every drug prescribed in the SHI system.[50] The dataset also contains information on the producer and the status of the drug as a generic or original drug with or without patent protection. For the analysis conducted in this thesis, several active ingredients were chosen from the dataset.

---

[49] See § 35b SGB V

[50] Defined Daily Doses (DDDs) are a WHO statistical measure of drug consumption used to standardize the comparative usage of various drugs between themselves or between different health care environments.

The use of the INSIGHT Health data has some advantages. Firstly, the dataset covers 99 % of the SHI prescription drug market. The risk for misleading results because of a bias in database is small. Secondly, the SHI drug market can be analyzed in more detail as the dataset is not limited to certain active ingredients.

The second dataset, provided by a large German sickness fund, includes information on the complete prescription history of patients and their physicians between January 2004 and December 2007 on a monthly basis for three different indications. The identity of patients and physician was made anonymous. The dataset also includes socio economic variables like age, gender and the employment status of patients, as well as information on the nature and the dispatch date of the drug. In contrast to the first dataset, this so-called routine data represents only a share of the SHI market. Since only the dataset of a singular sickness fund was available – even though it comprises a large number of members (>1.5 million insured persons) – the results could be biased. This is due to the historically determined differences in the sickness funds risk profiles, as before 1993, each sickness fund contracted specific population subgroups.[51] Therefore, the dataset from a singular sickness fund cannot be regarded as representative for the overall German population.[52] Thus, the results of the analysis in Chapter III should to be interpreted considering this limitation.

The third dataset was created from different sources. As regulative instruments are the main focus of the thesis, a dataset was constructed containing information on the inclusion of drugs in rebate contracts,[53] reference price groups[54] and the

---

[51] For example, the TK (Techniker Krankenkasse) contracted only individuals with technical professions like engineers or master craftsmen.

[52] See Holle *et al.* (2005), p. 308

[53] Information provided by INSIGHT Health

[54] Information provided by the G-BA and the German Institute of Medical Documentation and Information (*Deutsches Institut für Medizinische Dokumentation und Information*, DIMDI*)*

corresponding possible exemption from patient related co-payments.[55] Drugs with active ingredients which were part of the lead compound regulation were also identified through the framework agreement between sickness funds and the National Association of Statutory Health Insurance. The third dataset is connected to the first and the second one through the central pharmaceutical number (PZN) that identifies a drug uniquely within the SHI system.

Information about prices and discounts in Chapter VI were provided by the Lauer-Taxe® database from LAUER-FISCHER. Like the data set form INSIGHT Health, it holds information for every PZN about prices, discounts and characteristics of pharmaceutical products.

All econometric analysis in Chapter III were conducted using the STATA 10.1® software package (StataCorp LP), including the user-written command "margeff".[56] For the theoretical analyses of rebate contracts (Chapter IV) and early benefit evaluations (Chapter VI) Mathematica 5.0® was applied.

II.3 References

Anonym (2011): Festbetrag für Escitalopram gekippt. *Ärzte Zeitung online.* December 13th 2011. http://www.aerztezeitung.de/politik_gesellschaft/berufspolitik/article/683392/festbetrag-escitalopram-gekippt.html?sh=2&h=-1979661284 [Accessed: October 1st 2014].

Bartus T (2005): Estimation of marginal effects using margeff. *Stata Journal* 5(3), 309-329. http://www.stata-journal.com/article.html?article=st0086.

Bouvy J & Vogler S (2013): Background Paper 8.3 Pricing and Reimbursement Policies: Impacts on Innovation. Update on 2004 Background Paper. May 23th 2013. *Priority Medicines for Europe and the World "A Public Health Approach to Innovation"*. WHO Collaborating Centre for Pharmaceutical Policy and Regulation. http://www.who.int/medicines/areas/priority_medicines/BP8_3_pricing.pdf [Accessed: October 6th 2014].

BPI [Bundesverband der Pharmazeutischen Industrie e.V.] (2000 et sqq.): Pharma-Daten. [*Annual Report*] Berlin. http://www.bpi.de/daten-und-fakten/pharmadaten/ [Accessed: October 9th 2014].

---

55 Information provided by the *GKV-Spitzenverband*

56 See Bartus (2005)

Bump JB (2010): The Long Road to Universal Health Coverage: A Century of Lessons for Development Strategy. October 19th 2010. Seattle, WA: PATH, Rockefeller Foundation. http://www.rockefellerfoundation.org/uploads/files/23e4426f-cc44-4d98-ae81-ffa71c38e073-jesse.pdf [Accessed: October 9th 2014].

Bundesministerium für Gesundheit (ed.) (2014a): Gesetzliche Krankenversicherung Endgültige Rechnungsergebnisse 2013 (KJ1). June 25th 2014. Berlin. http://www.bmg.bund.de/fileadmin/dateien/Downloads/Statistiken/GKV/Finanzergebnisse/KJ1_2013.pdf [Accessed: October 9th 2014].

Bundesministerium für Gesundheit (ed.) (2014b): Gesetzliche Krankenversicherung Mitglieder, mitversicherte Angehörige und Krankenstand Jahresdurchschnitt 2013 (KM1). March 31st 2014. Berlin. http://www.bmg.bund.de/fileadmin/dateien/Downloads/Statistiken/GKV/Mitglieder_Versicherte/KM1_JD_2013.pdf [Accessed: August 27th 2014].

Bundesregierung (2014): Neue Bemessungsgrenzen für 2015. November 28th 2014. Berlin. http://www.bundesregierung.de/Content/DE/Artikel/2014/10/2014-10-15-rechengroessen-sozialversicherung.html [Accessed: August 22nd 2015].

Bundestagsdrucksache 17/10156. Beschlussempfehlung und Bericht des Ausschusses für Gesundheit (14. Ausschuss). June 27th 2012. Köln: Bundesanzeiger Verlagsgesellschaft. http://dip21.bundestag.de/dip21/btd/17/101/1710156.pdf [Accessed: October 6th 2014].

Busse R & Blümel M (2014): Germany: health system review. *Health Systems in Transition* 16(2), 1-296. ISSN: 1817-6127. http://www.euro.who.int/__data/assets/pdf_file/0008/255932/HiT-Germany.pdf [Accessed: August 22nd 2014].

Cassel D & Ulrich V (2014): AMNOG-Schiedsstelle: Schlichter oder Richter? Schiedsamtliche Preisermittlung bei neuen Arzneimitteln jenseits von Angebot und Nachfrage. [*Working Paper*] Juni 2014. *Wirtschaftswissenschaftliche Diskussionspapiere No. 03-14.* Universität Bayreuth. ISSN: 1611-3837.

EvaluatePharma (2014): World Preview 2014, Outlook to 2020. June 2014. Evaluate Ltd. http://www.evaluategroup.com/public/Reports/EvaluatePharma-World-Preview-2014.aspx [Accessed: October 8th 2014].

G-BA [Gemeinsamer Bundesauschuss] (2014): The Federal Joint Committee. Berlin. http://www.english.g-ba.de/ [Accessed: October 9st 2014].

Giuliani G, Selke G & Garattini L (1998): The German experience in reference pricing. *Health Policy* 44(1), 73-85. DOI: 10.1016/S0168-8510(98)00012-8.

Häussler B & de Millas C (2014): Arzneimittelausgaben der gesetzlichen Krankenversicherung im Jahr 2013 im Überblick. Kapitel 2. In: Häussler B, Höer A & Hempel E. Arzneimittel-Atlas 2014. Der Arzneimittelverbrauch in der GKV. Berlin, Heidelberg: Springer-Verlag, 3-48.

Holle R, Behrend C, Reitmeir P & John J (2005): Methodenfragen der Nutzung von GKV-Routinedaten für Kostenanalysen. In: Swart E & Ihle P. Routinedaten

im Gesundheitswesen. Handbuch Sekundärdatenanalyse: Grundlagen, Methoden und Perspektiven. Bern: Hans Huber, Hogrefe AG, 301-318. ISBN: 978-3456842370.

Institut der deutschen Wirtschaft (2013): Die Pharmazeutische Industrie in Deutschland - Ein Branchenportrait. 2nd revised Edition. Köln: Verband Forschender Arzneimittelhersteller (vfa), http://www.vfa.de/download/branchenportrait.pdf [Accessed: October 8th 2014].

Janning M (2010): Eine neue Generation von Verträgen. *Pharmazeutische Zeitung*. 10/2010. http://www.pharmazeutische-zeitung.de/index.php?id=32968 [Accessed: October 5th 2014].

Kanavos P, Nicod E, Espin J & van den Aardweg S (2010): Short- and Long-Term Effects of Value-Based Pricing vs. External Price Referencing. *EMiNet*. European Commission. http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/valuebased_pharmapricing_012010_en.pdf [Accessed: August 23rd 2014].

KBV [Kassenärztliche Bundesvereinigung] (2007): Bekanntmachungen: Rahmenvorgaben nach § 84 Absatz 7 SGB V und Vereinbarung nach § 84 Abs. 7a SGB V – Arzneimittel – für das Jahr 2007 vom 19. September 2006. *Deutsches Ärzteblatt International* 104(1-2), A69-A72. http://www.aerzteblatt.de/int/article.asp?id=54060 [Accessed: October 11th 2015].

KBV [Kassenärztliche Bundesvereinigung] (2014): Rahmenvorgaben nach § 84 Absatz 7 SGB V – Arzneimittel – für das Jahr 2015 vom 26. September 2014. http://www.kbv.de/media/sp/Rahmenvorgaben_Arzneimittel.pdf [Accessed: October 11th 2015].

Landschek I (2011): Vorteile für alle Beteiligten. *Pharmazeutische Zeitung*. 08/2011. http://www.pharmazeutische-zeitung.de/index.php?id=36951 [Accessed: October 5th 2014].

Paris V & Belloni A (2013): Value in Pharmaceutical Pricing. *OECD Health Working Papers No. 63*. OECD Publishing. DOI: 10.1787/5k43jc9v6knx-en.

Schlette S & Hess R (2013): Early benefit assessment for pharmaceuticals in Germany: lessons for policymakers. *The Commonwealth Fund* 29(October), 1-10. http://www.commonwealthfund.org/Publications/Issue-Briefs/2013/Oct/Early-Benefit-Assessment-for-Pharmaceuticals-in-Germany.aspx [Accessed: August 22nd 2014].

Stargardt T, Schreyögg J & Busse R (2005): Arzneimittelfestbeträge: Gruppenbildung, Preisberechnung mittels Regressionsverfahren und Wirkungen. *Das Gesundheitswesen* 67, 468-477. DOI: 10.1055/s-2005-858485.

Statistisches Bundesamt (ed.) (2014a): Ergebnisse der Bevölkerungsfortschreibung auf Grundlage des Zensus 2011. Wiesbaden. https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand/Tabellen/Zensus_Geschlecht_Staatsangehoerigkeit.html;jsessionid=2D08D745BA5DEB25EC9C0A1A82B1B213.cae2 [Accessed: August 27th 2014].

Statistisches Bundesamt (ed.) (2014b): Gesundheit - Ausgaben. Fachserie 12 Reihe 7.1.1 - 2012. Wiesbaden. https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitsausgaben/AusgabenGesundheit.html [Accessed: August 27th 2014].

Thomson S & Mossialos E (2004): Influencing Demand for Drugs through Cost Sharing. Chapter 13. In: Mossialos E, Mrazek M & Walley T. Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality. *European Observatory on Health Systems and Policies Series*. Maidenhead: Open University Press, 227-244. http://www.euro.who.int/__data/assets/pdf_file/0008/98432/E83015.pdf [Accessed: October 13th 2014].

Tuomi M, Rémuzat C, Vataire A-L & Urbinati D (2013): External Reference Pricing of Medicinal Products: Simulation-Based Considerations for Cross-Country Coordination. Final Report. December 2013. Brussels: European Commission. http://ec.europa.eu/health/healthcare/docs/erp_reimbursement_medicinal_products_en.pdf [Accessed: August 23rd 2014].

vfa [Verband Forschender Arzneimittelhersteller] (2011): Selektives Kontrahieren im Arzneimittelmarkt. [*Position Paper*] January 20th 2011. Berlin. http://www.vfa.de/de/wirtschaft-politik/positionen/pos-rabattvertraege [Accessed: October 5th 2014].

Wallace LS (2013): A view of health care around the world. *The Annals of Family Medicine* 11(1), 84. DOI: 10.1370/afm.1484.

III. Changes in drug dispense. Which factors determine what drug a patient receives?[57]

III.1 Introduction

In the German Statutory Health Insurance (SHI) System, patients often face switches of the drug dispensed to them. In the past, most these changes occurred between more expensive original drugs and bio-equivalent cheaper generic versions of the same active ingredient. The existing literature has found various determinants that affect these changes. Both, patient and physician characteristics, do play a role for the exchange of an original drug by a generic version, as shown by Hellerstein (1998), Coscelli (2000), and Decollogny et al. (2011). Furthermore the importance of the price differential between original and generic drugs has been shown.[58] Also, the impact of marketing activities on prescription behavior has been analyzed.[59]

However, the current literature is less extensive concerning switches between drugs of similar active ingredients and changes between generic drugs of the same active ingredients. In addition, the impact of regulatory instruments in the SHI system on the probability of a change in the dispensed drug has been analyzed to a lesser extent.[60]

---

[57] This part of the thesis is a joint work with Robert Haustein. Both authors contributed in equal parts to the development of the model and its empirical evaluation. Lead author of the manuscript was Robert Haustein.

[58] See Lundin (2000) and Furu et al. (2008)

[59] See Janakiraman et al. (2008)

[60] Furu et al. (2008) and Lundin (2000) incorporated aspects of regulative regimes in their analysis. In both cases, the considered regulatory instruments were similar to the German Reference Price system.

Unlike in other OECD countries with a smaller market share of generic drugs,[61] generic drugs are common in the German SHI prescription drug market. In 2009, 81 % of the dispensed active ingredients for which generic drugs were available, were generic drugs.[62] Only 19 % were original drugs without patent protection.[63] Thus, the relevance of drug switches from original to generic drugs is smaller in the German SHI market than in other OECD countries. In opposite, drug changes between generic drugs consisting of the same active ingredient are more present in the German SHI system than in countries with a lower generic drug share. Also the German drug market has a relatively high number of regulative instruments to encourage switches to cheaper active ingredients, whereas other European health systems prefer direct control by statutory pricing and positive lists.[64] Examples for such instruments are therapeutic reference pricing and the lead compound rule. Both instruments will be explained in detail in Section III.2.

Including these aspects in our analysis, we consider changes between drugs of the same active ingredient as well as changes between drugs of different, however pharmacologically similar, active ingredients. Avoiding possible misleading results due to changes based on different side effects of drugs, the therapeutic groups used in the analysis include only active ingredients that have a very similar range of side effects. Therefore, switches of drugs with different active ingredients resulting from side effects should only happen exceptionally.

The aim of this study is to estimate the effects of patient, physician, and drug specific characteristics on the prescription behavior of physicians. The paper contributes to the existing literature in various ways. First, while other authors narrow the focus on switches from original to generic drugs of the same active

---

61 See Mrazek and Frank (2004) and Decollogny et al. (2011)

62 The overall market share of generics in 2009 was 63 %. See Pro Generika e.V. (2010)

63 See Pro Generika e.V. (2010)

64 See Vogler et al.(2008), p. 59 and p. 85

ingredient, we extend the analysis to include drug switches between generic drugs and switches between similar active ingredients.

Second, the large dataset includes at least 200,000 observations of prescriptions by physicians for each of the different therapeutic groups of drugs. Moreover, the analysis is conducted for three therapeutic groups separately with very similar results. Therefore a high degree of validity and robustness of our results can be assumed.

Third, the impact of the implementation of several important regulative instruments in the German SHI system on the probability for a drug switch will be estimated in this paper. Similar studies have been concluded for a singular instrument in the Swedish drug market by Lundin (2000) and in the Norwegian drug market by Furu et al. (2008), however only in the context of prescription changes of original to generic drugs. Yet, we are not aware of any study examining the effects of the implementation of regulative instruments in the German SHI market on changes of the prescription behavior of physicians. Thus, this study tries to close this gap.

The results of the paper show that patient and physician specific characteristics and habits have a strong impact on the likelihood for a change of the dispensed drug. Patient specific characteristics like the time span between prescriptions or the number of previous changes between drugs of the same or different active ingredients increase the probability of a drug change. In contrast, the number of visited physicians, the age of the patient and the previous number of drug prescriptions within an active ingredient have an negative effect on the likelihood of a drug change. Also, the preferences of physicians for a specific producer or active ingredient influence the probability of a drug switch. The preference for an specific active ingredient increases the probability of drug switch while the preference for a specific producer reduces it. Moreover, the price difference between two consecutively dispensed drugs has an impact on the likelihood of a prescription change. In addition, the nature of the active ingredient of the dispensed drug influences the drug choice. Several regulative instruments

(reference pricing, co-payment exemption for patients, and rebate contracts) also positively affect the probability for a change of the dispensed drug significantly.

The paper is organized as follows. Section III.2 describes the German SHI market, the main regulative instruments, and the role of the physician. Section III.3 provides an overview of the existing literature on the prescription behavior of physicians. This is followed by the dataset prescription and the descriptive results in Section III.4. Section III.5 introduces a theoretical approach for the physician prescription behavior. Section III.6 discusses an empirical estimation framework based on the theoretical approach. Section III.7 shows the estimation results as well as their interpretations. Section III.8 concludes.

III.2 The German Health Care System

In 2009, over 90 % of the German citizens were insured in the German Statutory Health Insurance (SHI) system.[65] These insurees received both outpatient (ambulant care) and inpatient (hospital care) services in various forms.

The most important fields of services, in terms of expenditures for the SHI system, are prescription drug expenses in the outpatient sector (30.2 billion euro in 2010), medical services provided by physicians in ambulant care (27.1 billion euro in 2010), and hospital treatments for the insurees (58.1 billion euro in 2010).[66]

While prescription drugs are the second strongest driver of expenditures in the SHI system, they are the sector with the largest growth rate between 2000 and 2010. While the expenditures for medical services in ambulant care and hospital treatments increased on average about 2.1 % and 2.8 % per annum, the annually growth rate of expenditures for prescription drugs was higher (4.5 %). Thus,

---

65 See Bundesministerium für Gesundheit (2011) and Statistisches Bundesamt (2010)

66 See Bundesministerium für Gesundheit (2011)

between 2000 and 2010, the expenditures for prescription drugs rose stronger than the total health care expenditures (2.8 %).[67]

In response to the rising drug expenditures, the German Federal Ministry of Health, responsible for the regulation of the drug market, implemented various cost control instruments.[68] Interestingly, unlike in other OECD countries with fixed prices or price caps,[69] pharmaceutical companies in Germany are still allowed to set their manufacturer price freely.

One of the most important roles in the SHI system is full field by the physician in ambulant care. He inhabits a central role for both patient but also for the various regulation schemes. Since a core objective of our analysis is the measurement of the effects of the implementation of various regulative instruments on the prescription behavior of physicians, the most important schemes will be described in detail in the following.

The first restriction for a physician is the drug budget, implemented in 1989. However, the calculation process was changed over the years by various reforms. The current calculation procedure came into effect in 2001. Following this, a physician is only allowed to prescribe a restricted value of prescription drugs per patient and quarter. This value is measured in retail prices and depends on the age, the employment status (pensioner or employee), and the gender of the patient. The sum of the patient related prescription volumes form the drug budget of the physician.[70] In case of overstepping the drug budget a physician has to face consequences by the Regional Association of Statutory Health Insurance

---

67 See Bundesministerium für Gesundheit (2011)

68 See Denda (2010) for an overview of the regulative instruments in the SHI system.

69 See Mossialos et al (2004)

70 Physicians can shift drug budgets between patients. So they can use the idle budget of certain patients to subsidize other patients' drug demands.

Physicians.[71] These consequences range, depending on the amount of overstepping, from a formal discussion of the prescription behavior with the responsible RASHIP and the sickness funds to penalty payments equal to the difference between the drug budget and the values of the prescribed drugs in the quarter.

The second regulation instrument affecting the physician prescription decision is the "Aut-Idem" rule, implemented in 1989. This regulation scheme obliged pharmacists to substitute drugs by cheaper alternatives of the same active ingredient, if these are available in the same strength, package size and comparable form. Thus, it is possible that the drug a physician prescribes differs from the drug the patient receives from the pharmacist. However, physicians can prohibit the substitution by adding a reservation on the prescription.

The regulative instrument of reference pricing, first implemented in 1989, primarily targets the producers of drugs. It implements a maximum reimbursement limit for drugs that are part of a reference price group. As patients have to pay the positive difference between the reference price and the retail price, it seems reasonable that physicians try to prescribe drugs that do not require additional co-payments for patients. This is especially common for drugs where bioequivalent cheaper generic versions are available. At the same time, the prescription of cheaper drugs helps the physician to remain within the drug budget.

Since 2006 producers of drugs in specific reference price groups have the possibility to exempt their drugs from patient co-payments. To achieve this, pharmaceutical manufacturers have to lower their prices to a certain level below the reference price. The availability of these, cheaper, co-payment exempted drugs should affect both the prescription behavior of physicians due to the drug budget and the demand of patients for drugs without co-payments.

---

[71] The Regional Associations of Statutory Health Insurance Physicians (RASHIP) are responsible for the medical supply of compulsorily insured people. Each physician who wants to treat compulsorily insured persons has to be a member of the competent RASHIP.

Another regulation, implemented in 2007, is the "lead compound" rule. Included in the regional drug agreements between sickness funds and the Regional Association of Statutory Health Insurance Physicians, the lead compound rule promotes the prescription of specific active ingredients in selected therapeutic groups. This results in quotes for specific active ingredients that physicians are obliged to achieve in certain therapeutic groups.[72]

The latest major regulation scheme, also implemented in 2007, are rebate contracts between pharmaceutical producers and sickness funds. Following this regulation the Aut-Idem rule was modified. The pharmacies are now obliged to dispense primarily the rebated drug and not the cheapest drug. Consequently, physicians that persist on a specific drug for a patient, have to prohibit the substitution of the drug explicitly.

III.3 Literature review

The prescription decision of physicians was examined by various authors. However, the majority of the studies focused on prescription switches between brand name original drugs and corresponding generic versions.

Hellerstein (1998) used prescription data for multisource drugs from the US Food and Drug Administration[73] to examine determinants for the physicians' choices between generic drugs and branded originals. Her findings suggest that the preference of physicians for original brand name or generic drugs is fairly independent of observable patient specific characteristics. Thus, Hellerstein

---

[72] The rates are negotiated first at federal level and are modulated and/or expanded on the regional level in negotiations between the Regional Association of Statutory Health Insurance Physicians and the SHI sickness funds.

[73] The Food and Drug Administration (FDA) is an agency of the United States Department of Health and Human Services. It is one of the United States federal executive departments, responsible for the protection and promotion of public health through the regulation and supervision of, among other areas, prescription and over-the-counter pharmaceutical drugs (medications), and medical devices. The FDA is also responsible for the market access of new drugs and the withdraw of drugs from the US market in cases of serious side-effects that were unknown at the time of the product launch.

concludes that the heterogeneity in the prescription decision is due to unobserved physician characteristics. However, her analysis has several limitations. First, the dataset, which were extracted from a physician survey, included data of only two weeks. Thus only two observations for each patient existed. Due to the short observation period and the small number of observations it was difficult to measure possible patient or physician habits. Especially the analysis of patient specific habits is not possible as patients appear only twice in the dataset. Second, the data did not contain information on prices. Therefore the impact of possible price differences on prescription decisions could not be measured. At last, the dataset did not include information about which drug was finally dispensed to a patient but only about the drug the physician prescribed.

The paper of Coscelli (2000) addressed two of the limitations of Hellerstein's study. Coscelli's dataset included all prescriptions for anti-ulcer drugs for a 10 % sample of the population of Rome on a monthly base for the years 1990 - 1992. In addition, Coscelli had exact information about the drug that was finally dispensed to the patient. This avoids possible misleading results because of unobserved substitutions by the pharmacist. His results support Hellerstein's hypothesis of consistent physician related prescription habits, using a number of variables to describe the physician. However, in addition to Hellerstein's results, he also finds evidence for patient related characteristics, that affect the prescription choice of the physician. Yet, like Hellerstein, the paper of Coscelli does not include price data to describe the influence of the price differences on prescriptions.

Lundin (2000) fixed this issue by using data from two pharmacies in a small Swedish municipality of Tierp for the years 1992 and 1993. The dataset contained information about the prices of the dispensed drugs as well as the amount that had to be paid for a drug by both, the patient and a third-party payer. The dataset also included exact information about which drug was dispensed. The results of Lundin (2000) confirm the existence of habit persistence among both patients and physicians. In addition, it shows that the price difference between the original and the generic version of a drug has an effect on the prescription decision. Inherently,

an increase in the price difference results in an increasing frequency of physicians choosing the generic instead of the original drug.

Janakiraman et al. (2008) investigated the impact of promotion activities of pharmaceutical companies on the prescription decision of physicians. Their dataset included unique information on promotion related variables like the number of out-of-office meetings between physicians and representatives of pharmaceutical companies, symposium visits, and detailing visits by pharmaceutical representatives. The results indicate that a certain group of physicians, classified as "non-persistent" in their prescription behavior, are affected by detailing visits and by the number of symposium visits they are invited to. In opposite, physicians that are classified as "persistent" prescribers are only responsive to symposium visits. The results also imply that older doctors as well as physicians working in smaller practices are less likely to switch drug prescriptions. Physicians receiving more visits by pharmaceutical representatives, feature a higher willingness to change their drug prescriptions than physicians receiving fewer visits.

Furu et al. (2008) used a dataset from Norway, containing all prescriptions for 23 different active ingredients to determine explanatory factors for the prescription choice between original and generic drugs. Beside various patient and physician related variables, also price data was included in the estimation. The findings of the paper give further evidence on the importance of both physician and patient characteristics for the physician’s prescription decisions. The results indicate that the probability for generic substitution is affected by the price difference as well as by the type of insurance coverage of the patient. In addition, the study points out the role of pharmacies for the patient's decision to substitute the more expensive original drug by a cheaper generic product.

Stargardt (2010) analysed the impact of the inclusion of statins in the German reference price system on drug switches of long term users between the more expensive active ingredient atorvastatin and other statins. Using patient data of a large German sickness fund his results concerning patient related socio-economic

variables indicate that the probability of a patient to switch drugs decreases with older age and a larger number of hospital visits due to cardiovascular diseases in the baseline periods. Also patients with a high yearly income (> 41,800 euro) have a lower predicted probability to switch drugs compared to patients with a low income (< 15,000 euro). In contrast, the predicted probability for a drug switch increases for patients that are exempted from co-payments due to low income or unemployment. In addition, the membership in a disease management program for diabetes also increases the predicted probability for a drug switch.

Decollogny et al. (2011) examined the influence of patients, physicians, and certain generic drug market characteristics on the generic substitution in Switzerland. They used reimbursement data of a large health insurer for three regions in Switzerland during 2003. Their results indicate that poor health status (described by older patients and complex treatments) is associated with lower generic drug use. Increasing generic drug use is associated with higher out-of-pocket payments, greater price differences between generic and original drugs and with the number of generic drugs in the market.

Our own results and their relation to the presented literature will be discussed in the final Section III.8.

III.4 Dataset and descriptive results

The dataset is provided by a large German sickness fund with more than 1.0 million members during the observation period included in the dataset (2004 - 2007). It was one of the largest sickness funds in the SHI system (among the top 15 out of 241 considering the number of members in 2007).[74] The insured are from different social backgrounds and income groups. Compared to total SHI population, the age structure of the insurees is younger and the share of

[74] See Beiträge zur Gesellschaftspolitik (2008)

unemployed persons is below the average.[75] The catalogue of benefits and the reimbursement of physicians in the German SHI system is more or less identical over all sickness funds.[76] Consequently it seems unlikely that patients in our dataset are treated differently than patient in other sickness funds with a different age, mortality or gender structure.[77]

The data contains information about the complete prescription history of patients and their treading physicians between 2004 and 2007 on a monthly basis for three different therapeutic groups (HMG-CoA reductase inhibitors, ACE inhibitors, and proton pump inhibitors). The three therapeutic drug markets were chosen due to the high prevalence of the associated diseases and the significance of the associated expenditures for the SHI system. Also, each of the associated diseases is of chronic nature and requires constant treatment with drugs. Finally, all three therapeutic groups consist of active ingredients with and without patent protection.

The identity of patients and physician is made anonymous. Each patient is assigned a specific *patient_id*, while physicians are identified by a *prescriber_id* that is bestowed by the Regional Associations of Statutory Health Insurance Physicians. The dataset includes socio-economic variables like age, gender, and the status of the patient as an employed or an unemployed person. In addition, the data include information about the nature of the dispensed drug[78] (brand name, producer, strength, price per defined daily doses[79] and package size).

---

75 See Holle et al. (2005) for more information about the historically rooted risk profiles of different types of sickness funds.

76 See Schulze Ehring and Köster (2010)

77 See Grobe et al. (2005)

78 It has to be noted, that the prescribed drug and the dispensed drug can differ due to the "Aut-Idem" rule. We try to control this problem in our estimation using a specific variable that captures the effect of "Aut-Idem". See Section III.6.2.3.

79 The Defined Daily Doses (DDD) is a measurement for drug consumption. According to the definition by the WHO, it is “the assumed average maintenance dose per day

The initial overall dataset contains 2,617,017 observations for 73,032 physicians and 372,196 patients. We excluded patients in the dataset that received only one drug prescription in the observation period. Also, as the data contains some data errors, especially regarding invalid *prescriber_ids*, several observations had to be deleted. The two limitations reduced the number of observations included in the dataset only marginal (< 1 %).

Also, similar to other panel datasets of dynamic nature, the dataset suffers from the so-called initial conditions problem. The problem arises as we do not have any information on the behavior of patients and physicians before the observation period. Therefore we cannot observe possible important information that forms the prescription decision in the later, observable, time periods. Following the advices found in the literature (Heckman (1981) and Coscelli (2000)) to solve this problem, it is assumed that the prescription is either a first time treatment or that the treatment is restarted if a patient has not received a prescription in the therapeutic group for six months. This assumption seems suitable for our dataset, since it only includes chronic diseases that require constant drug treatments and a physician visit every three to six months.

Consequently, only those patients were included in the estimation who received their first prescription after June 2004. Resulting from the above mentioned restrictions the number of observations is reduced to 998,841, containing 62,024 physicians and 248,203 patients.

Table 1 shows the number of observations, patients and physicians for all three therapeutic drug markets. It also includes the number of drug switches during the observation period for each market.

for a drug used in its main indication in adults". See WHO Collaborating Centre for Drug Statistics Methodology (2011) for more information about the DDD system.

Table 1: Number of observations, patients, physicians and drug dispense changes

	HMG-CoA reductase inhibitors		ACE inhibitors		Proton pump inhibitors	
Variable name	**Number**	**%**	**Number**	**%**	**Number**	**%**
Observations	212,742	-	322,251	-	463,848	-
Patients	53,202	-	72,769	-	168,585	-
Physicians	29,783	-	35,841	-	53,315	-
Drug changes	45,393	21.3	58,803	18.2	80,973	17.5

Table 1 shows that at least 50,000 patients and at least nearly 30,000 physicians were observed in each therapeutic drug market. The total sum over all patients and physicians is not identical to the numbers given before, as some patients and physicians are part of more than one therapeutic group. The total number of observations ranged from slightly above 200,000 drug prescriptions for HMG-CoA reductase inhibitors to about 460,000 prescriptions for proton pump inhibitors. The percentage of drug switches ranged between 17.5 % and 21.3 % in the three therapeutic groups in the observation period of four years.

The three indications, representing different therapeutic drug markets, are described by the 4-digit ATC Code (also called ATC5 Code).[80] An individual active ingredient is identified by a unique 5-digit ATC Code (also called ATC7 Code)[81]. They are shown in Table 2.

The first therapeutic drug market are HMG-CoA reductase inhibitors (ATC5 Code C10AA, containing active ingredients C10AA**) that are used to control hypercholesterolemia and prevent cardiovascular diseases.

[80] The ATC code is an internationally used drug classification system. It is differentiated into five levels. The first level contains 14 main groups that are assigned to an anatomic main group (for example cardiovascular system) that is primarily affected by the drug. The next two levels describe the therapeutic group and its possible sub groups. The fourth and fifth level are classified by the chemical structure of the drug.

[81] See WHO Collaborating Centre for Drug Statistics Methodology (2010) for more information.

The second therapeutic group are ACE inhibitors for the treatment of hypertension and congestive heart failure. The market is defined by the ATC5 Code C09AA. It includes active ingredients with the ATC7 Codes C09AA**).

The third therapeutic group are proton pump inhibitors (ATC5 Code A02BC) that are used to reduce the gastric acid production to decrease the pain from heartburn. The included active ingredients are identified by the ATC7 Codes A02BC**).

Table 2 also shows drug expenditures for the active ingredients between 2004 and 2007. The market data (called Nationale Verordnungsinformation (NVI)) are provided by the German market research company INSIGHT Health.

Table 2: Market data of the observed therapeutic drug markets

Therapeutic group	**Active ingredient**	**7-digit ATC code**	**Sales in million € 2004**	**Sales in million € 2005**	**Sales in million € 2006**	**Sales in million € 2007**
HMG-CoA reductase inhibitors			**817.7**	**617.8**	**582.5**	**479.9**
	Simvastatin	C10AA01	286.6	375.3	374.8	352.9
	Lovastatin	C10AA02	18.0	14.3	11.9	8.5
	Pravastatin	C10AA03	83.6	78.6	74.5	44.3
	Fluvastatin	C10AA04	73.1	95.0	77.9	46.6
	Atorvastatin	C10AA05	356.4	54.6	43.4	27.6
ACE inhibitors			**557.2**	**575.1**	**480.5**	**356.6**
	Captopril	C09AA01	78.0	62.4	46.3	31.5
	Enalapril	C09AA02	201.5	198.9	163.5	115.1
	Lisinopril	C09AA03	107.1	104.5	90.8	59.1
	Perindopril	C09AA04	8.8	5.0	3.5	2.1
	Ramipril	C09AA05	118.0	167.6	150.5	131.1
	Quinapril	C09AA06	6.6	5.7	5.1	3.7
	Benazepril	C09AA07	11.4	9.6	6.7	4.7

	Cilazapril	C09AA08	2.8	2.3	1.8	1.1
	Fosinopril	C09AA09	11.7	9.5	6.7	4.9
	Trandolapril	C09AA10	1.6	1.1	0.8	0.5
	Spiralpril	C09AA11	7.8	6.8	3.7	2.1
	Moexipril	C09AA13	0.8	0.7	0.5	0.3
	Imidapril	C09AA16	1.1	1.0	0.6	0.4
Proton pump inhibitors			**993.7**	**1,090.1**	**993.0**	**985.1**
	Omeprazole	A02BC01	421.2	419.9	448.3	593.6
	Pantoprazole	A02BC02	297.4	354.1	286.9	204.1
	Lansoprazole	A02BC03	41.9	35.9	35.6	28.1
	Rabeprazole	A02BC04	13.4	15.0	12.5	10.5
	Esomeprazole	A02BC05	219.8	265.2	209.7	148.8

Source: NVI

It has to be noted that the econometric analysis was conducted separately for each therapeutic group to improve the validity of the results.

In the next step, we will develop a theoretical approach that formalizes the decision making process of physicians for a drug prescription in a therapeutic group.

III.5 A theoretical approach for the prescription behavior of physicians

In this section, a model for the decision making behavior of physicians will be developed. A basic assumption is that physicians act partly as agents of their patients. Thus, they care about the latter's health status. In case of indications where various related active ingredients are available, the physician has a scope of options that lead to similar medical results. Therefore, the physician has to choose which drug he wants to prescribe.

As mentioned before, the three therapeutic groups (HMG-CoA reductase inhibitors, ACE inhibitors, and Proton pump inhibitors) will be analyzed

separately; therefore we omit an additional index for the therapeutic group in our notion. Considering one therapeutic group, let $k = 1,..,K$ denote the drugs in this therapeutic group.

Let $DC_{ijkt} \in \{0,1\}$ denote whether a drug change to a drug *k* from any other drug in the therapeutic group has occurred $(DC_{ijkt} = 1)$ or not $(DC_{ijkt} = 0)$ by physician $j = 1,..,J$ for patient $i = 1,..,I$ in observation point $t = 1,..,T$.

In terms of panel data terminology, the physician is considered as the observed object with $j = 1,..,J$. He prescribes to his patient $i = 1,..,I$. The number of observed prescriptions to a specific patient is counted by $t = 1,..,T$. Therefore, the counting of observation points $t = 1,..,T$ is individual for each physician/patient tuple.

Note that drug changes between products of a singular producer, for example the exchange of a smaller package by a bigger one, are not considered as drug switches in our analysis. Consequently, the binary depending variable only takes the value of 1, if a drug change is connected to a change of the producer.

Let $U_{ijlkt}(DC_{ijlkt} = 1)$ denote the physician's utility from the drug switch such that he will change the medication if, and only if $U_{ijlkt}(DC_{ijlkt} = 1) > 0$.

In particular, we will assume that the physician's utility of a drug switch is additively decomposed into several components as follows:

$$U_{ijlkt}(DC_{ijlkt} = 1) = u_{ijlkt} + \varphi(p_{kt} - p_{lt-1}) + PC_{jkt} + D_{kt} + \tau_m \quad (1)$$

Where the following variables are used: u_{ijlkt} is a vector capturing patient specific variables; $\varphi(p_{kt} - p_{lt-1})$ describes the effect of retail prices on the physician's utility of a drug switch; the vector PC_{jkt} contains physician related variables; drug related attributes that could affect the prescription decision are included in the vector D_{kt}; the monthly time dummy $\tau_m \in \{1, \dots, 48\}$ captures possible observed month specific effects. Note the difference between the observation point *t* and the month *m*. The index *t* counts the number of prescriptions of a physician *j* for a specific patient *i*. In contrast, *m* is the month, in which the prescription occurs.

The distinction between these two subscripts becomes important for some of the variables used in the analysis.

The elements of equation (1) will be discussed and refined in turn in the following paragraphs.

In the case of multiple options for the medication of a medical condition with comparable effects, physicians take into account observable characteristics and attributes of the patient *i* for their prescription decisions. These are captured by the vector u_{ijlkt}. It includes patient specific characteristics like age or gender. Also, patient specific habits like the preference for a specific active ingredient are considered by the physician. The vector is parameterized as

$$u_{ijlkt} = \beta X_{ijlkt} + e_{ijlkt} \tag{2}$$

where X_{ijkt} is the vector of observable patient related variables.

The corresponding parameter vector is denoted as β, while the unobservable portion of the patient's term is represented by e_{ijlkt}. This residual is assumed to be independently and normally distributed over the observation points, patients, and physicians with $e_{ijkt} \in N(0,1)$.

Based on informational constrains and private motives, it cannot be assumed that physicians act as perfect agents for their patients. Thus, physicians will consider their own preferences and their information about available drugs.

An important aspect for the physician is the retail price of the prescribed drug. While patients are nearly fully reimbursed for drug expenditures, physicians have to consider the retail price of the prescribed drug due to their limited drug budget. The effect of the drug prices is estimated by the price difference between the dispensed drug $k \in \{1, \dots, K\}$ in observation point t and the dispensed drug $l \in \{1, \dots, K\}$, in observation point $t-1$ as $\varphi(p_{kt} - p_{lt-1})$, with $l \neq k$. The coefficient φ captures the effect of the price difference.[82]

[82] The price per DDD is used instead of the retail price to avoid possible miscalculations and misinterpretations. When using retail prices, the change of a

However, the retail price of a drug is only one of several factors affecting the prescription decision. It can be assumed that physicians also have a set of non-price related characteristics and habits concerning the prescription of drugs. For example, physicians might prescribe some drugs more frequently due to their specific patient clientele or their own preferences for a particular producer. Also, specialized physicians could have different drug preferences compared to general practitioners. The variable vector PC_{jkt} captures such physician specific characteristics and habits. It is parameterized as

$$PC_{jkt} = \lambda S_{jkt} + \alpha_j \tag{3}$$

The vector of observable physician characteristics and habits is denoted S_{jkt} with the corresponding parameter vector λ. The unobserved part of the physician preferences, assumed to be persistent over *t* and *k*, is denoted as α_j.

In addition to physician specific factors, we assume that physicians also consider drug specific properties in their prescription decision. Therefore the vector D_{kt} contains information about the active ingredient and the popularity of the drug. Also the possible effects of the implementation of regulation schemes targeting specific drugs are considered as a part of the drug specific variable vector. It is modeled as:

$$D_{kt} = \eta DV_{kt} + \chi RI_{kt} \tag{4}$$

where DV_{kt} is a vector of drug related variables. The implementation of regulation instruments that target drug *k* in observation point *t* is captured in vector RI_{kt}. The corresponding parameter vectors are η and χ.

Therefore, the empirical model to be estimated has the following form:

$$PR\left[DC_{ijlkt} = 1\right] = PR\left[\beta_0 + \beta X_{ijkt} + \varphi(p_{kt} - p_{lt}) + \lambda S_{jkt} + \eta DV_{kt} + \chi RI_{kt} + \tau_m + \alpha_j + e_{ijkt}\right] \tag{5}$$

drug that is related with a change in package size from a smaller package to a bigger one can result in a positive price difference, although the price per "pill" remains constant or even decreases. This problem is solved by the use of prices per DDD that make prices of drugs comparable and independent of package size or strength.

where $DC_{ijlkt} = 1$ if physician *j* changes the prescription to drug *k* from any other drug in observation point *t* for patient *i.*

III.6 Empirical analysis

III.6.1 Estimation strategy

First, it has to be decided, whether a logit or probit approach should be used to estimate equation (5). For both models, the unobserved heterogeneity can be assumed as a fixed or a random effect.

- In fixed effects models, α_j is considered as a parameter, which can be estimated like other parameter vectors. In this case, no assumption about the relationship between α_j and the other independent variables is specified.
- In random effect models, α_j is treated as a random variable, which is described by a density function.

The use of the fixed effect approach can lead to the incidental parameters problem.[83] This can result in non-consistent estimators for the unobserved heterogeneity when estimating a fixed effect probit model.[84] However, the estimated coefficients of a fixed effect logit model[85] are not biased as the conditional distribution of the model does not depend on the unobserved heterogeneity α_j.[86]

In opposite to the fixed effect model approaches, random effect models[87] assume that the correlation between the independent observed variables and the

---

[83] See Neyman and Scott (1948), Arellano (2003), and Wooldridge (2003), p. 490-492

[84] See Honoré (2002)

[85] See Chamberlain (1980)

[86] See Wooldridge (2003), p. 491

[87] See Heckman (1981)

unobserved heterogeneity α_j is zero. Similar to fixed effect models, both probit and logit models can be estimated. As simple estimators for the random effect logit model are not available,[88] the random effect probit model should be the preferred estimation approach.

Thus, the fixed effect logit model and the random effect probit model have been identified as suitable models for our estimation. Although the random effect probit model underlies stricter restrictions about the correlation between α_j and the independent, observable variables, it will be used to estimate equation (5). The reason is that the computation of a fixed effect logit model becomes excessive with a large number of observations. In addition, certain statistical problems arise in the calculation of partial effects in fixed effect logit models.[89]

The use of the random effect probit estimator leads to the correlation assumption of the following form $Corr(W_{ijkt}, \alpha_j) = 0$, where W_{ijkt} describes the variable vector containing all regressors of the model. This assumption is very stringent. Thus, a second empirical approach will be estimated that relaxes the correlation assumption.

In this second model, that follows Chamberlain (1980) and especially Mundlak (1978), the time-invariant unobserved heterogeneity α_j is allowed to correlate in linear form with the mean values of the time-varying regressors $\bar{W}_{ijk}$.[90] The unobserved effect α_j is assumed to have the linear form:[91]

$$\alpha_j = \kappa \overline{W}_{ijk} + \psi_j \qquad (6)$$

---

88 See Wooldridge (2003), p. 490

89 See Greene (1990), p. 656

90 See also Wooldrigde (2003), p. 487

91 The original approach, as it can be found in Wooldridge (2003), p. 487-490 and Mundlak (1978), contains a constant. Since we already included a constant in the random effect probit model, and both constants cannot be separated, we chose not to include the constant in equation (7).

The variable ψ_j is independent and normally distributed $\psi_j \backsim N(0, \sigma_\psi^2$. Also it is assumed that $E[\psi_j|\overline{W}_{ijk}] = E[\psi_j] = 0$ for all t. The modification of the random effect α_j leads to following model specification:

$$PR[DC_{ijkt} = 1] = PR[\beta_0 + \beta X_{ijkt} + \varphi(p_{kt} - p_{lt}) + \lambda S_{jkt} + \eta DV_{kt} + \chi RI_{kt} + \tau_m + \kappa \overline{W}_{ijk} + \psi_j + e_{ijkt} > 0] \quad (7)$$

Again, it should be remembered that the three therapeutic groups (HMG-CoA reductase inhibitors, ACE inhibitors, and proton pump inhibitors) will be analyzed separately.

III.6.2 Variable description

The dependent variable (SWITCH) is a binary variable, taking the value of 1, if patient *i* receives a drug *k* from physician *j* in observation point *t* that is different from the drug received in $t-1$, and 0 otherwise.[92] The different groups of independent variables are described in detail below. The selection of the included variables is based on various studies, especially Hellerstein (1998), Coscelli (2000), Lundin (2000), and Furu et al. (2008). In addition, if necessary, new variables were defined, f.e. to capture the effects of the implementation of regulatory instruments.

III.6.2.1 Patient related variables

The first category of independent variables are the patient related variables, shown in Table 3:

Table 3: Description of patient related independent variables

Variable name	Variable description
AGE	Age of the patient i

[92] The exact definition of a drug switch in terms of our analysis is formulated in Section III.5.

GENDER	Female = 1, male = 0
EAST GERMANY	Patient i receives treatment in East Germany = 1, Patient i receives treatment in West Germany = 0
WELFARE RECIPIENT	Patient i receives benefit payments in observation point t = 1, Patient i receives no benefit payments in observation point t = 0
NATIONALITY	Patient i is not a German citizen = 1, Patient i is a German citizen = 0
CITY AREA	Patient i lives in a city area = 1, Patient i lives in a rural area = 0
TIME LAPSE	Number of months between prescriptions in observation point t and t-1 for patient i
N PRESCRIPTIONS	Total number of prescriptions of the patient i
N ATC7 GROUPS	Total number of different ATC7 groups received by patient i
N PHYSICIANS	Number of different physicians that prescribed at least one drug to patient i
PAST SWITCHES BETWEEN ATC7 GROUPS	Number of switches between ATC7 group until observation point t for patient i
PAST SWITCHES WITHIN ATC7 GROUP	Number of drug switches within ATC7 group until observation point t for patient i
N PRESCRIPTIONS WITHIN ATC7 GROUP	Number of prescriptions within the same ATC7 group until observation point t for patient i

The first variables considered in the estimation process are the AGE and the GENDER of the observed patient. The location dummy EAST GERMANY captures possible differences in the prescription pattern between East and West Germany. The variable WELFARE RECIPIENT indicates whether a patient receives benefit payments by the government. NATIONALITY shows, whether the patient is a German citizen or not. CITY AREA describes whether the patient lives in a rural or in an urban area.

N PRESCRIPTIONS differentiates patients into heavy users (chronic users) and occasional users. The distinction of patients in heavy and light users is further described by the variable TIME LAPSE that counts the months between two following prescriptions of a drug in the therapeutic group, independent of the

visited physician. N ATC7 GROUPS counts the number of different active ingredients a patient has received over all observation points. The number can be influenced by both physician and patient. As the physician tries to find a suitable treatment for the patient, the number of different active ingredients in the sample can capture the difficulties to find one. In addition, the variable indicates the patient's willingness to change the treatment. N PHYSICIANS describes how many different physicians a patient has consulted during the observation period.

The next set of variables, also shown in Table 3, captures the persistence of patients to a specific drug or active ingredient. However, it has to be noted, that switches can also be affected by the choice of pharmacists or physicians, especially concerning the actually dispensed drug.

PAST SWITCHES BETWEEN ATC7 describes how many switches between different active ingredients a patient has experienced until observation point t. The variable N PRESCRIPTIONS WITHIN ATC7 GROUP, describes the continuous prescription of the same active ingredient until observation point t. The number of previous changes of the dispensed drug with an active ingredient is captured by the variable PAST SWITCHES WITHIN ATC7 GROUP.

III.6.2.2 Physician related variables

The next group of independent variables are the physician related covariates, described in Table 4.

Table 4: Description of physician related variables

Variable name	Variable description
N PATIENTS	Number of different patients that received at least one drug prescription from physician j
AGE PATIENTS	Average age of all patients that received at least one drug prescription from physician j
SPECIALIST	Physician j is a specialist = 1, physician j is a general practitioner = 0
QUANTITY PRESCRIPTIONS	Average quantity of prescriptions over the last 3 months of physician j
PERCENTAGE ATC7 GROUP	Average share of dispensed DDD of the

	prescribed active ingredient over the last 3 months (in percent) of physician j
HERFINDAHL-INDEX ATC7 GROUP	Herfindahl-Index across different active ingredients over the last 3 months (market shares measured in DDD) of physician j
HERFINDAHL-INDEX PRODUCERS	Herfindahl-Index across different producers over the last 3 months (market share measured in DDD) of physician j

The variables N PATIENTS and AGE PATIENTS are independent of the observation point t. They describe the total number of patients as well as the average age of patients that are treated by the physician, giving information about his patient clientele. They also capture possible experience effects resulting from the number of patients treated and age specific aspects for the prescription behavior of the physician. Possible differences between general practitioner and specialists are measured by the variable SPECIALIST.

QUANTITY PRESCRIPTIONS counts, for each observation point t, the average amount of defined daily doses (DDD) prescribed by the physician in the last three months. The variable separates doctors in heavy and light prescribers considering the specific therapeutic group. The importance of the dispensed active ingredient for the physician is indicated by the variable PERCENTAGE ATC7.

The variable HERFINDAHL-INDEX ATC7 GROUP describes the physician related diversity in prescribing different active ingredients for a specific indication.[93] The last physician related variable, HERFINDAHL-INDEX PRODUCERS captures possible preferences of physicians for specific drug producers.

III.6.2.3 Drug related variables

Table 5 shows drug specific variables that describe the properties of the dispensed drugs and the price difference between the dispensed drugs in observation point t and observation point t-1.

[93] The Herfindahl-Hirschman Index is the sum of squared market shares. For convenience the percentage values are multiplied with 100. The index ranges from 0 to 10,000.

Table 5: Description of drug related variables

Variable name	Variable description
PRICEDIFF	Price difference ((measured in price per DDD) between the dispensed drug in observation point t and the dispensed drug in observation point t-1 of patient i
MARKET SHARE PZN[94]	Market share of dispensed drug i (measured in DDD) related to the corresponding ATC7 group in observation point t of patient i (in percent)
ATC7 GROUP	Set of dummy variables, identifying the ATC7 group of the dispensed drug in observation point t of patient i
AUT-IDEM DRUG	Dummy variable with the value of 1, if dispensed drug is one of the 3 cheapest drugs of the active ingredient in observation point t of patient i, 0 if not

The variable PRICEDIFF captures the price difference (in price per DDD) between the dispensed drug in observation point t and its predecessor in t-1. MARKET SHARE PZN is an indicator for the popularity of a specific drug that is identified by its central pharmaceutical number (PZN). ATC7 GROUP is a set of dummy variables that captures drug specific effects based on characteristics of the corresponding active ingredient. The variable AUT-IDEM DRUG indicates, whether the dispensed drug was one of the three cheapest drugs within the corresponding active ingredient in observation point t. While the physician could have prescribed this drug explicitly, it is more likely that the pharmacist has exchanged the originally prescribed drug with the dispensed cheaper drug due to the Aut-Idem rule.

[94] The abbreviation PZN stands for the term "Pharma Zentral Nummer". The PZN is a 7-digit number, which identifies a drug clearly according to its name, pharmaceutical form, strength, and package size. Therefore, each drug in the Germany SHI market can be identified by its unique PZN.

III.6.2.4 Implementation of regulative instruments

The last group of variables contains indicators for the effect of the implementation of regulatory instruments on the probability of a change of the dispensed drug.

Table 6: Description of regulatory instruments

Variable name	Variable description
Definition of the variables concerning the implementation of regulatory instruments	Dummy variable, taking the value of 1 if, for the first time the dispensed drug in observation point t of patient i is part of the implemented regulatory instrument, while it was not in observation point t-1 of patient i, 0 otherwise.
LEAD COMPOUND	Describes the implementation of the lead compound rule.
REFERENCE PRICE	Describes the implementation of the reference price system.
EXEMPTION FROM CO-PAYMENT	Describes the implementation of the possibility to exempt drugs from patient related co-payments
REBATE CONTRACT	Describes the implementation of rebate contracts between health insurances and pharmaceutical producers

The variable LEAD COMPOUND displays the influence of the lead compound rule that encourages physicians to prescribe a specific active ingredient instead of other therapeutic options. Note that since the therapeutic market of ACE inhibitors was not covered by the lead compound rule, no coefficient was estimated for this therapeutic group. The dummy variable REFERENCE PRICE captures changes in prescription as a result of the introduction of the reference price system. The variables EXEMPTION FROM CO-PAYMENT and REBATE CONTRACT[95] measure the effects of introduction of the two latest regulatory reforms on the drug dispense situation of the patient. The former variable captures the effect of

[95] Since the dataset is restricted to a specific health insurance fund, only drugs which are part of rebate contracts of this health insurance fund are marked as rebated products.

the implementation of the possibility of drugs to become exempted from patient related co-payments. The latter dummy variable captures the impact of the introduction of a rebate contract between the pharmaceutical company and the health insurance fund.

The definition, whether a regulation instrument existed in the month the observation point falls into, is based on the status in the pharmacy software. This is due to the fact, that only with the implementation in the official pharmacy software; the regulations become relevant for the prescription decisions of the physicians and the dispensing decision of the pharmacists. An exception is the variable LEAD COMPOUND. Here the agreed inception of the treaty between the Association of Statutory Health Insurance Physicians and the sickness funds is considered.

The considered regulations were implemented with a time lap of at least a year. Consequently, the effects of the implementation of each regulatory instrument should not overlap. Still there is a minority of cases where two or three of the described regulation dummies change values simultaneously. Although the number of these cases is very small,[96] we deleted the concerned observations and recalculated the models. The estimations results did not differ; therefore the original dataset was used.

The descriptive statistics of the variables for each therapeutic market are shown in Appendix 1.

III.7 Estimation results

III.7.1 Random effect probit model

In this section, the results of the standard random effect probit model and of the random-effect probit model, inspired by Chamberlain (1980) and Mundlak

[96] The maximum of cases was found for the combination of co-payment exemption and rebate contacts. For this combination, in 1.8 % of the observed cases both dummy variables took the value of one in the same observation period.

(1978), are presented. Both models were estimated by using 50 evaluation points.[97] The stability of the models was checked by running the models with 34 and 66 evaluation points. Comparing the results, the relative differences between the coefficients are always <1 %. Thus, the models can be assumed to be stable.[98]

A likelihood-ratio test, conducted between the standard and the Chamberlain/Mundlak random effect probit models indicates that the latter econometric approach should be the preferred option.[99] This result is confirmed by the calculated AIC and BIC scores.[100]

The economic interpretation of the results of the Chamberlain/Mundlak probit model is limited to the magnitude and the sign of the coefficients. The results of the estimation are shown in Table 16 in Appendix 2.[101] It turns out that the estimation results of the three therapeutic groups are qualitatively very similar. Therefore, we describe the results for all three groups simultaneously.

It should be noted that in the following sections the term "probability of drug change" or similar expressions will be used. This is not entirely accurate. Following the model specification in Section III.5, the estimated coefficients for both the random effect probit models and the corresponding marginal effects have to be interpreted as effects on the "probability of a change to the drug in

---

97 See Butler and Moffitt (1982) and Hellerstein (1998) for more information about the derivation of the full likelihood for the random-effects probit model.

98 The stability was checked by using the quadchk command in Stata®. Results are available on request.

99 The results of the standard random effect probit model are shown in Table 15 in Appendix 2 in Section III.9.2.

100 AIC stands for the "Akaike Information Criterion", while BIC stands for the "Bayesian Information Criterion". Both criteria help to select a specific model within a class of parametric models that have a different number of parameters. Since the approaches are related, for both of them the rule can be stated, that the estimated model with the lower value of AIC or BIC should be chosen. For more information, see Akaike (1974) and Schwarz (1978).

101 To simplify the interpretation of the results, the estimated coefficients of the average values of the time variant variables as well as the estimates of the monthly dummy variables are not included. The results are available on request.

question". However, for reasons of readability, we will simply refer to "drug changes".

Patient related variables

The results of variables capturing the socio-economic status of patients indicate that the dispensed drug is less frequently switched for older patients than for younger patients (negative coefficient of AGE). The drug prescriptions of patients living in East Germany are more often switched than for patients living in West Germany (positive coefficient of EAST GERMANY). Both results can be found in all therapeutic areas. The gender of the patients has a negative impact on the switching probability. Therefore, women are less likely to get their drug prescription changed than man. However the effect is only significant for the therapeutic area of proton pump inhibitors. The variable CITY AREA is also only significant for ACE inhibitors, suggesting that drug prescriptions of patients living in larger cities are switched more often than for patients in rural areas of Germany.

The second set of patient related variables describe the habits and preferences of patients. The coefficient of TIMELAPSE is positive and significant for all therapeutic markets. It indicates that the longer the time gap between drug prescriptions, the more the dispensed drug of a patient is likely to get switched.

The total number of prescriptions a patient receives in the observation period (N PRESCRIPTIONS) has a significant positive effect on the drug change probability. Thus, patients receiving more prescriptions have a higher possibility to receive a different drug than patients with fewer prescriptions. Also the total number of different active ingredients (N ATC7 GROUPS) increases the likelihood of a drug change. This result is comprehensible, as patient that changes active ingredients more often automatically get their drug prescription changed more frequently.

The total number of different physicians a patient visits (N PHYSICIANS) has a negative effect on the switching probability. The positive coefficient of PAST SWITCHES BETWEEN ATC7 GROUPS indicates that patients who already had

different active ingredients prescribed in the past have an increased likelihood for prescription changes in the future. This effect is relatively small for patients treated with proton pump inhibitors compared to the two other therapeutic groups.

A similar explanation can be given for PAST SWITCHES WITHIN ATC7 GROUPS. Patients with a bigger variety of different drugs within an ATC7 group have an increased probability to get switched again in the future. This effect is stronger for patients with HMG-CoA reductase inhibitors.

The number of past prescriptions within an active ingredient (N PRESCRIPTIONS WITHIN ATC7 GROUP) has a negative effect on the drug change probability for all three therapeutic markets. Therefore patients that are adapted to a specific active ingredient, through a larger number of prescriptions in this group, are less likely to get switched to another drug than patients with a shorter prescription history concerning the specific ATC7 group. The smallest effect was estimated for patients treated with ACE inhibitors.

Summarizing the results for patient related variables, we find that for the group of socio-economic factors only age and whether the patient lives in East or West Germany have a significant impact on the switch probability for all three therapeutic areas. However, all variables describing the previous history of drug dispenses have significant effects on the probability of a drug switch.

Physician related variables

The results for variables describing the characteristics of physicians show that the total number of treated patients (N PATIENTS), their average age (AGE PATIENTS), and training of a physician as a specialist (SPECIALIST) have a negative impact on the probability of a drug switch. Thus, physicians that are specialists, have a high number of patients or an older patient clientele change drug prescriptions less often than physicians that are general practitioners, treating a lower number of patients or have a younger patient clientele.

The second set of variables captured the prescription habits of physicians. The results show that the probability of a drug switch is lower for patients treated by physicians with a higher number of average prescriptions (QUANTITY

PRESCRIPTIONS). A similar effect was found for patients receiving a drug with an active ingredient that is prescribed strongly by the corresponding physician (PERCENTAGE ATC7 GROUP). Both effects are not significant for the therapeutic group of ACE inhibitors.

The estimates of the Herfindahl coefficients indicate the effects of physician related preferences for specific active ingredients (HERFINDAHL-INDEX ATC7 GROUP) or producers (HERFINDAHL-INDEX PRODUCER) in a therapeutic group. The results show that physicians concentrating their prescriptions on a fewer number of active ingredients, expressed through a high HERFINDAHL-INDEX ATC7 GROUP, are more likely to change their prescription behavior than physicians prescribing across active ingredients.

It has to be noted that the negative sign of PERCENTAGE ATC7 GROUP and the positive sign of HERFINDAHL-INDEX ATC7 GROUP seems to be a contradiction. However, although the variables appear to be similar in their meaning, they capture different attributes of the physician. The variable PERCENTAGE ATC7 GROUP measures the physician related average market share (in DDD) of the actual dispensed active ingredient over the last three months. The results indicate that a physician who prescribes a large amount of this active ingredient changes his prescriptions less often. Thus, the variable captures the possible preference for the actual dispensed active ingredient.

In contrast, HERFINDAHL-INDEX ATC7 GROUP shows the overall preference of a physician towards the different active ingredients in the therapeutic market. It is, in contrast to PERCENTAGE ATC7 GROUP, independent of the actual dispensed active ingredient in observation point t. A physician that prefers to concentrate his prescriptions on a fewer number of active ingredients, measured by a high HERFINDAHL-INDEX ATC7 GROUP, has a higher probability to switch his prescriptions than a doctor prescribing a larger variety of active ingredients, expressed by a lower Herfindahl index.

At last, independent of the therapeutic markets, physicians preferring specific drug producers, indicated through a high HERFINDAHL-INDEX PRODUCER, are less likely to switch the prescriptions of their patients.

The analysis of the physician related variables indicates that characteristics of the physician and his patient clientele both have an impact on the probability of a drug switch. The effects are similar in all observed therapeutic markets. Also, prescription preferences for specific active ingredients or producers affect the prescription behavior of physicians significantly.

While it seems that both patient and physician specific characteristics and habits play a role for the drug dispense, the influence of the properties of the dispensed drugs itself are captured by the set of drug related variables.

Drug related variables

The estimated coefficient of the PRICE DIFFERENCE between the dispensed drugs in observation points t and $t-1$ is negative in all therapeutic groups. Therefore, in the case a cheaper drug in observation point t compared to the drug in observation point t-1 is dispended, the negative price difference has a positive effect on the switch probability. In the case of a positive price difference, which corresponds to dispending a more expensive drug in t compared to $t-1$, the effect is negative.

The market share of the prescribed drug has a significant negative impact on the probability of a drug change. This result has to be interpreted cautiously as it could be a statistical artifact. It is less likely that patients are switched to drugs with a high market share since a large number of patients already receive this drug. Therefore, the probability of a change towards such a drug is affected negatively. The positive coefficient of the AUT IDEM variable is not surprising, as most drugs dispensed with the attribute Aut-Idem are the result of a substitution process by the pharmacists.

The dummies for the active ingredients[102] in the therapeutic markets indicate that there are significant differences across the active ingredients in the frequency of drug changes. This shows that specific attributes (e.g. patent status) of the prescribed active ingredients have an effect on the choice of the dispensed drug.

The results of the estimation of the drug related variables showed that especially the price difference of drugs plays an important role. A negative price difference leads to a significant increase in the probability of a drug change, indicating the change from a more expensive drug to a cheaper one. Also the probability of a drug switch depends on the active ingredient of the dispensed drug.

Implementation of regulative instruments

The implementation of any regulative instrument considered had a positive impact on the probability of a drug change. The strongest impact was found for the implementation of rebate contracts (REBATE CONTRACTS) followed by reference pricing (REFERENCE PRICE) and the possibility to exempt drugs from patient co-payments (EXEMPTION CO-PAYMENT).

The statistic significant coefficients for the regulation variables indicate that beside patient, physician or drug related attributes, an additional impact on switches of the dispensed drug is the implementation of regulatory instruments.

III.7.2 Magnitude analysis

Since the coefficient estimates of the random effect probit models are very difficult to interpret in an economic sense, the marginal effects of the coefficients are estimated. Most papers[103] calculate the marginal effects at the means (MEM). Therefore, the sample means of the independent variables would be used as fixed values. Instead of using MEM, we computed the average of discrete or partial

---

[102] Note that the estimates for the active ingredient dummies have to be interpreted in comparison to the reference category.

[103] Examples for the use of MEM can be found in Hellerstein (1998), Coscelli (2000) and Lundin (2000). For the calculation of MEM in STATA®, see Bartus (2005).

changes over all observations, therefore estimating average marginal effects (AME).[104]

The main argument for the use of average marginal effects is the possibility of a more realistic interpretation of the results, especially for dummy variables.[105] Under the consideration of dummy variables, the calculation of MEM is delicate, as the used sample means refer to non-existing observations. Since the larger part of our independent variables are dummies, the use of AMEs is the preferred option.

The calculated AMEs have to be interpreted differently for continuous and dummy variables. For continuous variables, the AMEs indicate how a partial change (about 1 unit) of a variable changes the probability for the switch of the dispensed drug. The interpretation of marginal effects for dummy variables is different. They show the marginal impact on the probability for a drug dispense switch if the dummy variable changes its value from 0 to 1.

Table 7 shows the average marginal effects of patient related variables:

Table 7: Average marginal effects for patient related variables of the Chamberlain/Mundlak random probit model[106]

	Dependent variable – SWITCH					
	HMG-CoA reductase inhibitors		**ACE inhibitors**		**Proton pump inhibitors**	
Variable name	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**

[104] The average marginal effects were calculated using the user written command margeff in STATA®. See Bartus (2005)

[105] See Bartus (2005)

[106] Due to the complexity of the estimation and limitations in the calculating capacity, the marginal effects estimated for ACE inhibitors and proton pump inhibitors are based on an 80 % respectively 60 % sample. To confirm the results, we repeated the probit model estimation and drew several random samples (80 % or 60 % respectively) and calculated the marginal effects again. The results for the marginal effects do not differ much and are available on request.

AGE	-0.0257	***	0.0030	-0.0230	***	0.0023	-0.0113	***	0.0014
GENDER	-0.0014	***	0.0014	-0.0023	**	0.0011	-0.0003		0.0008
EAST GERMANY	0.0076		0.0021	0.0042	**	0.0017	0.0092	***	0.0015
WELFARE RECIPIENT	0.0128		0.0433	0.0165		0.0309	0.0018		0.0255
NATIONALITY	0.0061		0.0043	0.0004		0.0034	0.0016		0.0021
CITY AREA	0.0001		0.0016	0.0003		0.0014	0.0039	***	0.0011
TIME LAPSE	0.0178	***	0.0003	0.0168	***	0.0003	0.0123	***	0.0002
N PRESCRIPTIONS	0.0092	***	0.0005	0.0070	***	0.0003	0.0024	***	0.0001
N ATC7 GROUPS	0.0553	***	0.0037	0.0552	***	0.0035	0.0764	***	0.0012
N PHYSICIANS	-0.0424	***	0.0011	-0.0361	***	0.0009	-0.0312	***	0.0006
PAST SWITCHES BETWEEN ATC7 GROUPS	0.1580	***	0.0044	0.1733	***	0.0049	0.0847	***	0.0012
PAST SWITCHES WITHIN ATC7 GROUP	0.1471	***	0.0012	0.1025	***	0.0009	0.0544	***	0.0006
N PRESCRIPTIONS WITHIN ATC7 GROUP	-0.0360	***	0.0009	-0.0230	***	0.0005	-0.0236	***	0.0003

*** indicates significance on the 1 % level, ** significance on the 5 % level and * shows significance on the 10 % level

The results indicate that for a one unit increase in the age of the patient (AGE) the likelihood for a switch of the dispensed drug decreases between 1.1 and 2.6 %. This shows that older patients are less likely to face a drug change than younger patients. Concerning the number of months between prescriptions (TIME LAPSE), we find that an increase of about one month increases the probability of a drug change for the patient between 1.2 and 1.8 %. Visiting one additional physician in the observation period (N PHYSICIANS) decreases the change probability on average about 3.1 to 4.2 %.

The increase of the previous number of switches between active ingredients (PAST SWITCHES BETWEEN ATC7 GROUPS) about one unit raises the switch probability between 8.5 and 17.3 %. An additional past drug switch within

an active ingredient (PAST SWITCHES WITHIN ATC7 GROUPS) increases the likelihood of a drug switch between 5.4 and 14.7 %.

If patients receive drugs more constantly within a specific active ingredient (N PRESCRIPTIONS WITHIN ATC7 GROUP), the probability of a switch decreases between 2.3 and 3.6 % for each additional previous prescription within this active ingredient. Table 8 shows the average marginal effects for the physician related variables.

Table 8: Average marginal effects for physician related variables of the Chamberlain/Mundlak random probit model

Dependent variable – SWITCH						
	HMG-CoA reductase inhibitors		**ACE inhibitors**		**Proton pump inhibitors**	
Variable name	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**
N_PATIENTS	-0.0008 ***	0.0002	-0.0007 ***	0.0001	-0.0007 ***	0.0000
AGE PATIENTS	-0.0004 ***	0.0001	-0.0003 ***	0.0001	-0.0004 ***	0.0001
SPECIALIST	-0.0046 ***	0.0016	-0.0060 ***	0.0014	-0.0071 ***	0.001
QUANTITY PRESCRIPTIONS	-0.0055 ***	0.0015	-0.0012	0.001	-0.0037 ***	0.0007
PERCENTAGE ATC7 GROUP	-0.0005 ***	0.0001	0.0001	0.0001	-0.0006 ***	0.0001
HERFINDAHL-INDEX ATC7 GROUP	0.00001 ***	0.0001	0.00001 ***	0.0001	0.00002 ***	0.0001
HERFINDAHL-INDEX PRODUCERS	-0.00002 ***	0.0001	-0.00003 ***	0.0001	-0.00004 ***	0.0001

*** indicates significance on the 1 % level, ** significance on the 5 % level and * shows significance on the 10 % level

For the group of physician related variables, the dimension of the variables has to be considered, before interpreting the impact of a one unit change. While some marginal changes are highly significant in a statistical sense, the actual importance of such a change is rather low. An example is the average age of the patients

treated by the physician in the observation period (AGE PATIENTS). Even if the average age would increase about ten years, the effect would still be lower than 1 %.

Since the issue of the dominance of statistical significance in contrast to substantive significance has already been discussed by various authors (e.g. Hoover and Siegler (2008); Ziliak and McCloskey (2008); and Miller (2008)), it will be not addressed here in detail. Considering the underlying dimensions and the relation to the mean values of the variables that can be found in Table 12 in Appendix 1, only a number of physician related marginal effects are regarded as substantively significant.

Therefore only the Herfindahl indices seem to have a considerable impact on the dependent variable. At first glance, the actual effect of the Herfindahl indices on the change probability seems relatively small. Still, the effects should not be underestimated, as the coefficient only indicates the probability increase of a drug change if the Herfindahl-Hirschman-Index (HHI) increases about one unit. As the Herfindahl indices can take values up to 10,000, the small impact on the change probability of an increase about one unit are misleading.[107]

Following the results in Table 8, an increase of the HHI measuring the preference of physicians for a specific active ingredient (HERFINDAHL INDEX ATC7 GROUPS) raises the probability for a drug switch. The probability decreases for patients whose physicians show a high preference for specific drug producers (HERFINDAHL INDEX PRODUCERS). Both effects are strongest for the group of proton pump inhibitors.

The average marginal effects of drug related variables on the SWITCH variable are shown in Table 9.

[107] See Miller (2008) for more information about misleading interpretation of marginal effects because of different scales.

Table 9: Average marginal effects for drug related variables of the Chamberlain/Mundlak random probit model

Dependent variable – SWITCH						
	HMG-CoA reductase inhibitors		**ACE inhibitors**		**Proton pump inhibitors**	
Variable name	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**
PRICEDIFF	-0.1568 ***	0.0068	-0.2150 ***	0.0069	-0.0339 ***	0.0020
MARKET SHARE PZN	-0.0038 ***	0.0002	-0.0003 ***	0.0001	-0.0019 ***	0.0001
AUT-IDEM DRUG	0.0561 ***	0.0042	0.0447 ***	0.0048	0.0404 ***	0.0031
ATC_C10AA01	0.0088	0.0065	-	-	-	-
ATC_C10AA02	Reference category		-	-	-	-
ATC_C10AA03	0.0229 ***	0.0070	-	-	-	-
ATC_C10AA04	-0.0500 ***	0.0061	-	-	-	-
ATC_C10AA05	-0.0660 ***	0.0068	-	-	-	-
ATC_C09AA01	-	-	0.0424	0.0293	-	-
ATC_C09AA02	-	-	0.0459	0.0285	-	-
ATC_C09AA03	-	-	0.0598 **	0.0302	-	-
ATC_C09AA04	-	-	-0.0669 ***	0.0231	-	-
ATC_C09AA05	-	-	0.0332	0.0266	-	-
ATC_C09AA06	-	-	0.0442	0.0304	-	-
ATC_C09AA07	-	-	-0.1746	1.2351	-	-
ATC_C09AA08	-	-	0.0158	0.0275	-	-
ATC_C09AA09	-	-	-0.0519	0.0435	-	-
ATC_C09AA10	-	-	-0.0089	0.0259	-	-

ATC_C09AA11	-	-	-0.1746	0.3350	-		-
ATC_C09AA13	-	-	-0.1746	1.2351	-		-
ATC_C09AA16	-	-	Reference category		-		-
ATC_A02BC01	-	-	-	-	-0.0318	***	0.0032
ATC_A02BC02	-	-	-	-	-0.0522	***	0.0027
ATC_A02BC03	-	-	-	-	-0.0096	**	0.0038
ATC_A02BC04	-	-	-	-	Reference category		
ATC_A02BC05	-	-	-	-	-0.0570	***	0.0027

*** indicates significance on the 1 % level, ** significance on the 5 % level and * shows significance on the 10 % level

The results of the marginal effects of the drug related variables show that the price difference seems to have a large impact on the probability of a drug change. The effect has to be interpreted differently for positive and negative price differences. The prescription of a cheaper (more expensive) drug in t compared to the drug in t-1 would lead to an average rise (decrease) of the switch probability between 3.4 and 21.5 % for an increase of the price per DDD about one euro. While this effect seems very large, it has to be noted, that the average price difference lies between 0.02 euro and 0.04 euro. Following this, the actual effect has to be considered much weaker.[108] A dispended drug that falls under the Aut-Idem rule increased the probability of a drug change between 4.0 and 5.6 %.

If the patient receive the HMG-CoA reductase inhibitor atorvastatin (ATC7 Code C10AA05), the likelihood of a drug switch decreases about 6.6 % in comparison to the reference active ingredient lovastatin (ATC7 Code C10AA02). In case of fluvastin (ATC7 Code C10AA04), the decrease is 5.0 %.

It has to be noted that during the observation period the active ingredients atorvastatin and fluvastin have been under patent protection whereas for lovastatin (ATC7 Code C10AA02), simvastatin (ATC7 Code C10AA01) and pravastatin

[108] This is a further example for the importance of substantive significance as mentioned by Hoover and Siegler (2008), Ziliak and McCloskey (2008) and Miller (2008)

(ATC7 Code C10AA03) generic versions were available. Thus, the results show that the probability for drug switches increases whether a physician changes the prescription to or within an active ingredient for which generic drugs are available.

The same holds for the therapeutic group of the ACE inhibitors. We find that patients treated with perindopril (ATC7 Code C09AA04) have a decreased probability (-6.7 %) for a change in their drug dispense. In opposite, for patients using lisinopril (ATC7 code C09AA03) the likelihood of a drug switch increases about 6 % compared to the reference active ingredient imidapril (ATC7 Code C09AA16).

In case of proton pump inhibitors, the results indicate that a drug change to or within one of the active ingredients with existing generics (omeprazole (ATC7 Code A02BC01), pantoprozole (ATC7 Code A02BC02), and lansoprazole (ATC7 Code A02BC03) is less likely than a change to or within the patent protected reference active ingredient rabeprazole (ATC7 Code A02BC04). The relative high probability for a switch to or within rabeprazole compared to the active ingredients with available generic drugs is unusual for a patent drug. The reason seems to be the relative high market share of parallel imports for rabeprazole during the observation period. In contrast, there are no parallel importers in the market for the patent protected active ingredient esomeprazole (ATC7 Code A02BC05). The results indicate that patients receiving esomeprazole have a reduced likelihood to experience a change in drug prescription (-5.7 %) compared to the reference drug rabeprazole.

Table 10 describes the average marginal effects of the introduction of major regulatory instruments between 2004 and 2007 on the probability of a drug switch.

Table 10: Results of the Chamberlain/Mundlak random effect probit estimation for the effects of the introduction of regulatory instruments

Dependent variable – SWITCH									
	HMG-CoA reductase inhibitors			ACE inhibitors			Proton pump inhibitors		
Variable name	**Coefficient**		**Standard Error**	**Coefficient**		**Standard Error**	**Coefficient**		**Standard Error**
LEAD COMPOUND	0.7962		50.3801	Not included in regulatory regime			0.8361		429.2979
REFERENCE PRICE	0.1124	***	0.0062	0.0542	**	0.0312	0.0577	***	0.0039
EXEMPTION FROM CO-PAYMENT	0.0088	**	0.0033	0.0638	***	0.0028	0.0791	***	0.0030
REBATE CONTRACT	0.2492	***	0.0048	0.4209	***	0.0048	0.3461	***	0.0045

*** indicates significance on the 1 % level, ** significance on the 5 % level and * shows significance on the 10 % level

The last category of covariates captures the effects of the implementation of regulatory instruments on the changes of the dispensed drug for patients. The results show, that the introduction of reference prices (REFERENCE PRICE) increased the probability for a change in the dispensed drug between 5.4 and 11.2 %. The introduction of the possibility for pharmaceutical companies to exempt their drugs from patient co-payments (EXEMPTION FROM CO-PAYMENT) also increased the probability for a drug switch between 0.9 % and 7.9 %. The implementation of rebate contracts had the largest impact on the likelihood of a drug switch. The probability increased between 24.9 and 42.1 % following the implementation of rebate contracts.

III.8 Discussion

The aim of this paper was to estimate the effects of patient, physician and drug related characteristics and habits on the probability of a switch of the dispensed drugs for chronic diseases in the German SHI system. Moreover, for the first time,

the impact of the implementation of regulative instruments in the German SHI system on the probability of drug switches was analyzed.

We evaluated the effects of the patient, physician, and drug related variables for three different therapeutic groups, namely, HMG-CoA reductase inhibitors, ACE inhibitors and proton pump inhibitors. These therapeutic groups range quite prominently among the treatments of chronic diseases. We used a dataset consisting of the prescription history of over 50,000 patients and an overall number of nearly one million drug prescription observations between January 2004 and December 2007.

Interestingly, the estimated effects are similar for all three therapeutic groups. Thus, our results seem to be quite robust, even more so in view of the fairly large datasets.

The results indicate that patient and physician specific characteristics and habits have a significant impact on the probability of a drug switch. In line with Hellerstein (1998) and Stargardt (2010), our results suggest that older patients are less often switched than younger patients. Similar to Coscelli (2000), we find that an increase in time between treatment episodes increases the probability of a drug switch. Also, patients with a higher total number of different active ingredients, a larger account of previous switches between active ingredients, and especially more previous drug changes within and between active ingredients are more likely to get switched in their prescription.

Contrary to the results of Coscelli (2000), patients visiting a greater number of different doctors have a reduced probability of a drug switch. A possible explanation is that a new physician has to assemble medical knowledge about the patient first. Therefore the physician will initially prescribe the drug previously prescribed by his predecessor to avoid possible side effects.

Considering physician related habits and characteristics, the results indicate that patients face an increased probability for a drug switch if their physician prefers specific active ingredients. A reason for this could be an increased knowledge of the physician concerning the active ingredient, leading to a better knowledge

about the range of drugs on the market to choose from. In contrast, patients treated by physicians that have a strong preference for a specific manufacturer are changed less likely.

The analysis also shows that a cheaper price of the dispensed drug and the fact that it is an Aut-Idem drug (i.e. among the three cheapest drugs of an active ingredient) increase the probability to switch to this drug significantly. Both results show that physicians include economic aspects in their decision making, obviously to evade possible punishment due to regulations like budgeting.

In the existing literature, the impact of regulatory instruments on the prescription decision of physicians has only been investigated by few authors (e.g. Furu et al. (2008) and Lundin (2000)). Since the German SHI prescription drug market is strongly regulated, we included variables to capture the effects of the implementation of regulative regimes. The results show that the introduction of reference pricing, the possible exemption from patient co-payments, and especially the implementation of rebate contracts had a strong positive impact on the likelihood for a switch to a drug included in these instruments.

Overall, we find strong evidence that patient and physician related characteristics and habits influence the probability for a drug switch for patients in the German SHI market. In addition, the results indicate a strong impact of economic factors on the prescription behavior of physicians. Especially the implementation of several regulative instruments increased the likelihood of a drug switch significantly.

In contrast to similar theoretical approaches, we do not incorporate parameters that represent the level of reimbursement by the sickness funds.[109] The reason is that prescription drugs in the German SHI system are nearly fully reimbursed. Patients only have to pay a small co-payment between five and ten euro. Therefore the question of cost sharing between the two parties is less important.

[109] See Hellerstein (1998) and Lundin (2000)

However, the importance of drug prices for the physician due to the drug budget is acknowledged in the estimation process.

The dataset includes only data of one specific (although large) health insurance fund. This could influence the representativity of the results. Especially the low number of unemployed persons in the data set should be noted. However, due the structure of the SHI system, the supply of health care services is irrespective of the income of the insuree. Therefore, the possible bias should be small. Unfortunately, an extension of the data sample is difficult, as most health insurance funds do not share patient related data, even for scientific research.

For further research it would be interesting to include information about marketing activities of pharmaceutical companies (e.g. number of visits by pharmaceutical representatives) in the German SHI system. Following Venkataraman and Stremersch (2007) and Janakiraman et al. (2008) such factors could have an impact on the prescription decision. Also further variables regarding doctors' characteristics, such as age or practice type (e.g. singular or group practice) are desirable. Finally, it would be interesting to analyze whether the income situation of patients affect the prescription behavior of physicians.

III.9 Appendix

III.9.1 Appendix 1

Table 11: Descriptive statistics of patient related variables

	HMG-CoA reductase inhibitors				**ACE inhibitors**				**Proton pump inhibitors**			
Variable name	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**
AGE	60.62	11.02	0	99	58.97	13.21	0	102	52.00	16.01	0	101
GENDER	0.38	0.49	0	1	0.38	0.48	0	1	0.51	0.50	0	1
EAST GERMANY	0.15	0.36	0	1	0.16	0.37	0	1	0.13	0.34	0	1

WELFARE RECIPIENT	0.01	0.02	0	1	0.01	0.02	0	1	0.01	0.02	0	1
NATIONALITY	0.03	0.17	0	1	0.03	0.17	0	1	0.05	0.21	0	1
CITY AREA	0.34	0.47	0	1	0.33	0.47	0	1	0.30	0.46	0	1
TIME LAPSE	3.06	3.49	0	41	2.55	2.88	0	41	1.95	3.79	0	41
N PRESCRIPTIONS	6.64	3.90	2	38	7.98	5.19	2	38	6.86	6.52	2	62
N ATC7 GROUPS	1.19	0.43	1	4	1.07	0.27	1	3	1.42	0.62	1	5
N PHYSICIANS	1.42	0.70	1	7	1.48	0.75	1	8	1.60	0.88	1	11
PAST SWITCHES BETWEEN ATC7 GROUPS	0.13	0.40	0	9	0.05	0.25	0	9	0.33	0.77	0	14
PAST SWITCHES WITHIN ATC7 GROUP	0.88	1.33	0	35	1.05	1.52	0	17	0.97	1.67	0	27
N PRESCRIPTIONS WITHIN ATC7 GROUP	3.57	2.81	1	38	4.39	3.73	1	38	3.36	4.74	1	62

Table 12: Descriptive statistics of physician related variables

	HMG-CoA reductase inhibitors				**ACE inhibitors**				**Proton pump inhibitors**			
Variable name	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**
N_PATIENTS	9.42	13.54	1	191	11.42	15.04	1	206	17.66	30.72	1	468
AGE PATIENTS	61.66	7.21	1	94	60.33	8.43	0	98	52.71	9.30	0	96
SPECIALIST	0.31	0.46	0	1	0.29	0.45	0	1	0.34	0.47	0	1
QUANTITY PRESCRIPTIONS	3.48	2.14	0.33	49.33	3.99	2.48	0.33	38.67	3.83	2.37	0.33	42.67
PERCENTAGE ATC7 GROUP	84.18	25.83	0.28	100.00	68.49	31.02	0.32	100.00	75.34	30.29	0.17	100.00
HERFINDAHL-INDEX ATC7 GROUP	8,360	2,226	2,000	10,000	6,629	2,685	1,528	10,000	7,686	2,498	2,000	10,000
HERFINDAHL-	6,227	3,046	761	10,000	5,737	2,970	830	10,000	6,220	2,938	933	10,000

INDEX
PRODUCERS

Table 13: Descriptive statistics of drug related variables

	HMG-CoA reductase inhibitors				ACE Inhibitors				Proton pump inhibitors			
Variable name	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**
PRICEDIFF	-0.03	0.10	-2.83	2.01	-0.02	0.07	-3.42	2.00	-0.04	0.20	-7.99	8.03
MARKET SHARE PZN	4.71	8.23	0.00	51.12	4.70	7.92	0.00	98.55	4.77	6.67	0.00	36.3
AUT-IDEM-DRUG	0.11	0.31	0	1	0.03	0.18	0	1	0.14	0.34	0	1
ATC_C10AA01	0.78	0.41	0	1	-	-	-	-	-	-	-	-
ATC_C10AA02	0.01	0.12	0	1	-	-	-	-	-	-	-	-
ATC_C10AA03	0.09	0.29	0	1	-	-	-	-	-	-	-	-
ATC_C10AA04	0.07	0.26	0	1	-	-	-	-	-	-	-	-
ATC_C10AA05	0.04	0.19	0	1	-	-	-	-	-	-	-	-
ATC_C09AA01	-	-	-	-	0.05	0.22	0	1	-	-	-	-
ATC_C09AA02	-	-	-	-	0.27	0.44	0	1	-	-	-	-
ATC_C09AA03	-	-	-	-	0.15	0.36	0	1	-	-	-	-
ATC_C09AA04	-	-	-	-	0.00	0.04	0	1	-	-	-	-
ATC_C09AA05	-	-	-	-	0.51	0.50	0	1	-	-	-	-
ATC_C09AA06	-	-	-	-	0.01	0.08	0	1	-	-	-	-
ATC_C09AA07	-	-	-	-	0.01	0.08	0	1	-	-	-	-
ATC_C09AA08	-	-	-	-	0.00	0.03	0	1	-	-	-	-
ATC_C09AA09	-	-	-	-	0.01	0.07	0	1	-	-	-	-
ATC_C09AA10	-	-	-	-	0.00	0.02	0	1	-	-	-	-
ATC_C09AA11	-	-	-	-	0.00	0.05	0	1	-	-	-	-
ATC_C09AA13	-	-	-	-	0.00	0.02	0	1	-	-	-	-
ATC_C09AA16	-	-	-	-	0.00	0.02	0	1	-	-	-	-

ATC_A02BC01	-	-	-	-	-	-	-	-	0.57	0.49	0	1
ATC_A02BC02	-	-	-	-	-	-	-	-	0.22	0.41	0	1
ATC_A02BC03	-	-	-	-	-	-	-	-	0.03	0.16	0	1
ATC_A02BC04	-	-	-	-	-	-	-	-	0.01	0.11	0	1
ATC_A02BC05	-	-	-	-	-	-	-	-	0.17	0.37	0	1

Table 14: Descriptive statistics of regulatory instruments

	HMG-CoA reductase inhibitors				**ACE inhibitors**				**Proton pump inhibitors**			
Variable name	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**
LEAD COMPOUND	0.01	0.08	0	1	-[110]	-	-	-	0.02	0.12	0	1
REFERENCE PRICE	0.04	0.19	0	1	0.00	0.02	0	1	0.02	0.15	0	1
EXEMPTION FROM CO-PAYMENT	0.10	0.30	0	1	0.09	0.28	0	1	0.06	0.23	0	1
REBATE CONTRACT	0.08	0.28	0	1	0.06	0.24	0	1	0.05	0.21	0	1

III.9.2 Appendix 2

Table 15: Results of the standard random effect probit model

Dependent variable -SWITCH						
	HMG-CoA reductase inhibitors		**ACE inhibitors**		**Proton pump inhibitors**	
Variable name	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**	**Coefficient**	**Standard Error**
Patient related variables						
AGE	-0.0006	0.0005	-0.0002	0.0003	-0.024 ***	0.0002
GENDER	-0.0802	0.0085	-0.0099	0.0072	-0.0043	0.006

[110] The proton pump inhibitors were not part of the lead compound regime.

EAST	0.0462	***	0.0125	0.0352	***	0.011	0.0771	***	0.0106
WELFARE RECIPIENT	0.0615		0.246	0.1170		0.1798	0.0112		0.179
NATIONALITY	0.0357		0.025	0.0038		0.0212	0.0048		0.0148
CITY AREA	-0.0026		0.0096	-0.0024		0.0087	0.0264	***	0.0077
TIME LAPSE	0.0918	***	0.0014	0.0938	***	0.0012	0.0849	***	0.0009
N PRESCRIPTIONS	0.0303	***	0.0019	0.0268	***	0.0012	0.0249	***	0.0008
N ATC7 GROUPS	0.1376	***	0.0172	0.1301	***	0.0182	0.3309	***	0.0069
N PHYSICIANS	-0.2800	***	0.0068	-0.235	***	0.0054	-0.2373	***	0.0041
PAST SWITCHES BETWEEN ATC7 GROUPS	0.4387	***	0.0161	0.4818	***	0.0178	0.2709	***	0.0048
PAST SWITCHES WITHIN ATC7 GROUP	0.6887	***	0.0046	0.5564	***	0.0032	0.3886	***	0.003
N PRESCRIPTIONS WITHIN ATC7 GROUP	-0.2158	***	0.0031	-0.1584	***	0.002	-0.1655	***	0.0018
Physician related variables									
N_PATIENTS	-0.001	***	0.001	-0.0085	***	0.0007	-0.0068	***	0.0003
AGE PATIENTS	-0.0096	***	0.0009	-0.003	***	0.0006	-0.005	***	0.0004
SPECIALIST	-0.02	***	0.01	-0.0384	***	0.0091	-0.0447	***	0.0078
QUANTITY PRESCRIPTIONS	-0.013	**	0.0061	0.0039		0.0042	-0.0229	***	0.0031
PERCENTAGE ATC7 GROUP	-0.0025	***	0.0004	-0.0001		0.0002	-0.0012	***	0.0002
HERFINDAHL-INDEX ATC7 GROUP	0.00005	***	0.0001	0.0001	***	0.0001	0.0001	***	0.0001
HERFINDAHL-INDEX PRODUCERS	-0.0001	***	0.0001	-0.0001	***	0.0001	-0.0002	***	0.0001
Drug related variables									
PRICEDIFF	-0.6938	***	0.0342	-1.0271	***	0.0356	-0.2198	***	0.012

MARKET SHARE PZN	-0.0133	***	0.0009	-0.0008		0.0006	-0.0163	***	0.0007
AUT-IDEM DRUG	0.14	***	0.0169	0.1763	***	0.0193	0.0656	***	0.0147
ATC_C10AA01	0.1031	***	0.038	-		-	-		-
ATC_C10AA02	Reference category			-		-	-		-
ATC_C10AA03	0.1295	***	0.0383	-		-	-		-
ATC_C10AA04	-0.3004	***	0.0435	-		-	-		-
ATC_C10AA05	0.6129	***	0.0532	-		-	-		-
ATC_C09AA01	-		-	0.4661	***	0.1434	-		-
ATC_C09AA02	-		-	0.481	***	0.1424	-		-
ATC_C09AA03	-		-	0.5541	***	0.1426	-		-
ATC_C09AA04	-		-	-0.4221	**	0.204	-		-
ATC_C09AA05	-		-	0.4163	***	0.1426	-		-
ATC_C09AA06	-		-	0.4425	***	0.1485	-		-
ATC_C09AA07	-		-	0.2535	*	0.1497	-		-
ATC_C09AA08	-		-	-6.6225		8448.975	-		-
ATC_C09AA09	-		-	0.2678	**	0.1495	-		-
ATC_C09AA10	-		-	-0.1773		0.3453	-		-
ATC_C09AA11	-		-	-0.073		0.1655	-		-
ATC_C09AA13	-		-	-7.5212		14014.42	-		-
ATC_C09AA16	-		-	Reference category			-		-
ATC_A02BC01	-		-	-		-	-0.1805	***	0.0244
ATC_A02BC02	-		-	-		-	-0.3727	***	0.0244
ATC_A02BC03	-		-	-		-	-0.0347		0.0287
ATC_A02BC04	-		-	-		-	Reference category		
ATC_A02BC05	-		-	-		-	-0.4788		0.0265
Regulatory instruments									

LEAD COMPOUND	8.3961		16280.15	Not included in regulatory regime			13.645		75122.87
REFERENCE PRICE	0.5152	***	0.024	0.2821	**	0.1403	0.3533	***	0.0179
EXEMPTION FROM CO-PAYMENT	0.0961	***	0.0173	0.3883	***	0.0125	0.6223	***	0.0133
REBATE CONTRACT	1.2066	***	0.0153	1.6827	***	0.0142	1.668	***	0.014
Controls									
Monthly Dummies	Yes			Yes			Yes		
Constant (β_0)	-1.3511	***	0.0903	-1.4963	***	0.163	-1.6894		0.0826
Log Likelihood	-67938.25			-104034.13			-126519.41		
Rho	0.061		0.0033	0.088		0.0029	0.081		0.0024
Number Observations	212,742			322,048			463,848		

*** indicates significance on the 1 % level, ** significance on the 5 % level and * shows significance on the 10 % level

Table 16: Results of the Chamberlain/Mundlak random effect probit estimation for patient related variables

Dependent variable -SWITCH									
	HMG-CoA reductase inhibitors			**ACE inhibitors**			**Proton pump inhibitors**		
Variable name	**Coefficient**		**Standard Error**	**Coefficient**		**Standard Error**	**Coefficient**		**Standard Error**
Patient related variables									
AGE	-0.1521	***	0.0179	-0.1413	***	0.0138	-0.0806	***	0.0102
GENDER	-0.0084		0.0085	-0.0141	**	0.0071	-0.0018		0.0060
EAST	0.0447	***	0.0122	0.0257	**	0.0106	0.0642	***	0.0104
WELFARE RECIPIENT	0.0738		0.2451	0.0980		0.1771	0.0129		0.1800
NATIONALITY	0.0360		0.0247	0.0025		0.0206	0.0115		0.0148
CITY AREA	0.0008		0.0094	0.0019		0.0083	0.0279	***	0.0075

TIME LAPSE	0.1052	***	0.0019	0.1034	***	0.0016	0.0877	***	0.0012
N PRESCRIPTIONS	0.0546	***	0.0028	0.0427	***	0.0019	0.0173	***	0.0010
N ATC7 GROUPS	0.3269	***	0.0220	0.3374	***	0.0210	0.5372	***	0.0081
N PHYSICIANS	-0.2509	***	0.0068	-0.2213	***	0.0052	-0.2220	***	0.0042
PAST SWITCHES BETWEEN ATC7 GROUPS	0.9260	***	0.0256	1.0353	***	0.0284	0.5937	***	0.0081
PAST SWITCHES WITHIN ATC7 GROUP	0.8628	***	0.0077	0.6218	***	0.0054	0.3852	***	0.0042
N PRESCRIPTIONS WITHIN ATC7 GROUP	-0.2127	***	0.0051	-0.1412	***	0.0032	-0.1679	***	0.0022
Physician related variables									
N_PATIENTS	-0.0049	***	0.0011	-0.0044	***	0.0008	-0.0046	***	0.0003
AGE PATIENTS	-0.0026	***	0.0008	-0.0021	***	0.0006	-0.0032	***	0.0004
SPECIALIST	-0.0271	***	0.0097	-0.0370	***	0.0088	-0.0513	***	0.0076
QUANTITY PRESCRIPTIONS	-0.0323	***	0.0092	-0.0073		0.0063	-0.0262	***	0.0052
PERCENTAGE ATC7 GROUP	-0.0031	***	0.0005	0.0005		0.0003	-0.0043	***	0.0003
HERFINDAHL-INDEX ATC7 GROUP	0.0001	***	0.0001	0.0001	***	0.0001	0.0001	***	0.0001
HERFINDAHL-INDEX PRODUCERS	-0.0001	***	0.0001	-0.0002	***	0.0001	-0.0003	***	0.0003
Drug related variables									
PRICEDIFF	-0.9287	***	0.0405	-1.3205	***	0.0427	-0.2415	***	0.0141
MARKET SHARE PZN	-0.0226	***	0.0012	-0.0020	**	0.0008	-0.0139	***	0.0010
AUT-IDEM DRUG	0.3073	***	0.0209	0.2523	***	0.0247	0.2665	***	0.0184
ATC_C10AA01	0.0525		0.0382	-		-	-		-

ATC_C10AA02	Reference category			-			-		-		
ATC_C10AA03	0.1313	***	0.0383	-			-		-		-
ATC_C10AA04	-0.3247	***	0.0442	-			-		-		-
ATC_C10AA05	-0.4498	***	0.0547						-		-
ATC_C09AA01	-		-	0.2406			0.1531		-		-
ATC_C09AA02	-		-	0.2682	*		0.1522		-		-
ATC_C09AA03	-		-	0.3368	**		0.1523		-		-
ATC_C09AA04	-		-	-0.4958	**		0.2120		-		-
ATC_C09AA05	-		-	0.2041			0.1524		-		-
ATC_C09AA06	-		-	0.2483			0.1572		-		-
ATC_C09AA07	-		-	0.0559			0.1585		-		-
ATC_C09AA08	-		-	-7.4554			19601.71		-		-
ATC_C09AA09	-		-	0.1581			0.59		-		-
ATC_C09AA10	-		-	0.3577			-1.02		-		-
ATC_C09AA11	-		-	0.1659			-0.34		-		-
ATC_C09AA13	-		-	-7.553			22793.93		-		-
ATC_C09AA16	-		-	Reference category					-		-
ATC_A02BC01	-		-	-			-		-0.2223	***	0.0246
ATC_A02BC02	-		-	-			-		-0.4037	***	0.0246
ATC_A02BC03	-		-	-			-		-0.0701	**	0.0288
ATC_A02BC04	-		-	-			-		Reference category		
ATC_A02BC05	-		-	-			-		-0.4577	***	0.0269
Regulatory instruments											
LEAD COMPOUND	8.9284		32,639	Not included in regulatory regime					13.9348		134,174
REFERENCE PRICE	0.5672	***	0.0271	0.2992	**		0.1563		0.3612	***	0.0216
EXEMPTION FROM CO-	0.0512	***	0.0189	0.3501	***		0.0135		0.4741	***	0.0154

PAYMENT									
REBATE CONTRACT	1.0815	***	0.0174	1.6367	***	0.0161	1.5157	***	0.0156
Controls									
Monthly Dummies	Yes			Yes			Yes		
Constant (β_0)	-1.4636	***	0.0920	-2.0371	***	0.1701	-1.4683	***	0.0580
Log Likelihood	-66404.947			-99182.028			-123373.96		
Rho	0.045		0.003	0.067		0.0027	0.064		0.0022
Number Observations	212,742			322,048			463,848		

*** indicates significance on the 1 % level, ** significance on the 5 % level and * shows significance on the 10 % level

III.10 References

Akaike, H., (1974), "A New Look at the Statistical Model Identification.", *IEEE Transactions on Automatic Control*, Vol. 19, No. 6, 716-723.

Arellano, M., (2003), "Discrete Choices with Panel Data.", *Investigaciones Económicas*, Vol. 27, No. 3, 423-458.

Bartus, T., (2005), "Estimation of Marginal Effects using margeff.", *Stata Journal, StataCorp LP*, Vol. 5, No. 3, 309-329.

Beiträge zur Gesellschaftspolitik, (2008) "dfg-Ranking Liste der deutschen Krankenkassen." *Beiträge zur Gesellschaftspolitik*, Vol. 3, No. 1, 1-9.

Bundesministerium für Gesundheit, (2011), "Gesetzliche Krankenversicherung - Kennzahlen und Faustformeln 2011", http://www.bmg.bund.de/fileadmin/dateien/Downloads/Statistiken/GKV/Kennzahlen__Daten/GKV_Kennzahlen_Faustformeln_2011_Bund_09_2011.pdf [Accessed: October 28 2011].

Butler, J.S., Moffitt, R., (1982), "A Computationally Efficient Quadrature Procedure for the One-Factor Multinomial Probit Model.", *Econometrica*, Vol. 50, No. 3, 761-764.

Chamberlain, G., (1980), "Analysis of Covariance with Qualitative Data.", *Review of Economic Studies*, Vol. 47, No. 1, 225-238.

Coscelli, A., (2000), "The Importance of Doctors' and Patients' Preferences in the Prescription Decision.", *The Journal of Industrial Economics*, Vol. 48, No. 3, 349-369.

Decollogny, A., Eggli, Y., Halfon, P., Lufkin,T.M., (2011), "Determinants of Generic Drug Substitution in Switzerland.", *BMC Health Services Research*, Vol. 11, No. 17, 1-12.

Denda, R., (2010), "Steuerung im Arzneimittelbereich: Dreißig Instrumente in dreißig Jahren.", *Pharmazeutische Zeitung*, No. 10.

Furu, K., Dalen, D.M., Locatelli, M., Strom, S., (2008), "Generic Substitution", *Memoranda, University of Oslo, Department of Economics,* No. 11/2008.

Greene, W.H., (1990), "Econometric Analysis", 2nd Edition. *Macmillian*, New York.

Grobe, T., Ihle, P., (2005), "Versicherungsstammdaten und sektorüber-greifende Analyse." *In: Swart, E., Ihle, P., Routinedaten im Gesundheitswesen. Verlag Hans Humber*, Bern, 17-34.

Heckman, J. (1981), "Statistical Models for Discrete Panel Data." *In Mansiki, C. and McFadden, D. (Eds), Structural Analysis of Discrete Data, MIT Press,* Cambridge (MA), 114-178.

Hellerstein, J.K., (1998), "The Importance of the Physician in the Generic Versus Trade-Name Prescription Decision". *Rand Journal of Economics,* Vol. 29, No.1, 108-136.

Holle, R., Behrend, C., Reitmeir, P., John, J., (2005), "Methodenfragen der Nutzung von GKV-Routinedaten für Kostenanalysen." *In: Swart, E., Ihle, P., Routinedaten im Gesundheitswesen. Verlag Hans Humber*, Bern, 301-318.

Honoré, B.E., (2002), "Nonlinear Models with Panel Data", *Portuguese Economic Journal,* Vol. 1, No. 2, 163-179.

Hoover, K, and Siegler, M., (2008), "Sound and Fury: McCloskey and Significance Testing in Economics", *Journal of Economic Methodology,* Vol. 15, No. 1, 1-37.

Janakiraman, R. Dutta, S., Sismeiro, C, Stern, P., (2008), "Physicians' Persistence and its Implications for Their Response to Promotion of Prescription Drugs." *Management Science,* Vol. 54, No. 6, 1080-1093.

Lundin, D., (2000), "Moral Hazard in Physician Prescription Behavior". *Journal of Health Economics*, Vol. 19, No. 5, 639-662.

Miller, J. E., (2008), "The Goldilocks Principle: Avoiding Pitfalls in Interpretation of Regression Coefficients", *Rutgers, The State University of New Jersey - Institute for Health, Health Care Policy and Aging Research.*

Mossialos, E., Walley, T., Mrazek, M., (2004), "Regulating Pharmaceuticals in Europe: An Overview." *In: Mossialos, E., Walley, T., Mrazek, M., Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality, Open University Press*, Maidenhead, 1-37.

Mrazek, M., Frank, R., (2004), "The Off-Patent Pharmaceutical Market." *In: Mossialos, E., Walley, T., Mrazek, M., Regulating pharmaceuticals in Europe:*

striving for efficiency, equity and quality. Open University Press, Maidenhead, 245-259.

Mundlak, Y., (1978), "On the Pooling of Time Series and Cross Section Data.", *Econometrica*, Vol. 46, No. 1, 69-85.

Neyman, J., Scott, E.L., (1948), "Consistent Estimation from Chapterially Consistent Observations", *Econometrica*, Vol. 16, No. 1, 1-32.

Pro Generika e.V., (2010), "Marktdaten Januar – Dezember 2009", http://www.progenerika.de/de/generika/data/marktdaten/ims-dez09.html [Accessed: February 4th 2011].

Schulze Ehring, F., Köster, A.-D., (2010), "Beitrags- und Leistungsdifferenzierung in der GKV?". *WIP Diskussionspapier 3/10*, Wissenschaftliches Institut der PKV.

Schwarz, G. E., (1978), "Estimating the Dimension of a Model.", *Annals of Statistics*, Vol. 6, No. 2, 461–464.

Stargardt, T., (2010), "The Impact of Reference Pricing on Switching Behavior and Healthcare Utilization: The Case of Statins in Germany.", *European Journal of Health Economics*, Vol. 11, No. 3, 267-277.

Statisches Bundesamt Deutschland, (2010), "Bevölkerung 1950 - 2009", http://www.destatis.de/jetspeed/portal/cms/Sites/destatis/Internet/DE/Content/Statistiken/Zeitreihen/LangeReihen/Bevoelkerung/Content75/lrbev03a.psml [Accessed: November 30th 2010].

Venkataraman, S. and Stremersch, S., (2007), "The Debate on Influencing Doctors' Decisions: Are Drug Characteristics the Missing Link?", *Management Science*, Vol. 53, No. 11, 1688-1701.

Vogler S., Habl C., Leopold C., Rosian-Schikuta I., de Joncheere K., Thomsen TL., (2008), "PPRI Report", Vienna.

WHO Collaborating Centre for Drug Statistics Methodology, (2010), "Structure and principles", http://www.whocc.no/atc/structure_and_principles [Accessed: November 25th 2010].

WHO Collaborating Centre for Drug Statistics Methodology, (2011), "Definition and general considerations", http://www.whocc.no/ddd/definition_and_general_-considera/ [Accessed: February 25th 2011].

Wooldridge, J., (2003), "Econometric Analysis of Cross Section and Panel Data", *MIT Press*, Cambridge (MA), London.

Ziliak, S.T., McCloskey, D.N., (2008), "The Cult of Statistical Significance: How the Standard Error Costs US Jobs, Justice, and Lives", *University of Michigan Press*, Ann Arbor (MI)

IV. A microeconomic approach of rebate contracts in the German health care system[1]

IV.1 Introduction

Prescription drugs are one major source of expenditures in the German Statutory Health Insurance (SHI) system. About 19 % of the SHI budget is spent for prescription pharmaceuticals. The expenditures for prescription drugs have grown stronger since 2005 (5.3 % per year) than the expenditures for hospitals (3.6 %) and physicians (5.0 %).[2] To reduce the expenditures for prescription drugs, various instruments were implemented in the SHI system.[3]

Among others, rebate contracts are considered as a way to reduce health care expenditures. A rebate contract between a sickness fund (or a group of sickness funds) and a producer of pharmaceuticals contains agreements about rebates on every drug consisting of an active ingredient that is dispensed in a pharmacy at the expense of the sickness fund. The German health care system allows rebate contracts between pharmaceutical firms and sickness funds since 2003. Thereby, the extent of the contract is not specified. It can include only a singular product or the whole portfolio of a pharmaceutical firm. However, rebate contracts were not used frequently until 2007 as the incentives for pharmaceutical producers were rather low. Due to a legal change in 2007, pharmacists are legally obliged to dispense rebated products instead of other drugs with the same molecule. Since then, pharmaceutical producers receive a legal priority for the supply of insured of the sickness fund with their products. In return, they have to grant rebates on their products. Consequently, the popularity of rebate contracts increased. While

---

1 This part of the thesis is a joint work with Robert Haustein. Both authors contributed in equal parts to the development of the model and its elaboration. Lead author of the manuscript was Christoph de Millas.

2 See Bundesministerium für Gesundheit (2004-2009)

3 See Denda (2010)

physicians have the right to demand that a specific drug is dispensed, the denial of rebated drugs would affect their personal budget and they could be financially prosecuted for economic inefficiency.[4]

The economic effects of rebate contracts are still under discussion. Some parties argue that rebate contracts will increase competition and thereby reduce prices, since the current prices in the market include price mark-ups, resulting from price leadership and market domination of a few big generic producers. For supporters of these arguments the rebate contracts are an option to break this oligopoly structure.[5]

Other parties suggest that the rebate contracts will even increase the oligopolistic power in drug markets, as large firms will be able to offer a higher volume of rebates. Following this, they will be able to win the tenders. In the end, smaller producers will be driven out of the market and prices will rise again due to the increased concentration of the market.[6]

The goal of this paper is to analyze, with the help of a theoretical model, which of the two contrary opinions is more applicable.

Even though the concept of tendering is not uncommon in the pharmaceutical market,[7] the theoretical literature about rebate contracts in pharmaceutical markets is limited. So far, we are not aware of any paper that analyzed the German market for rebate contracts in a theoretical economic model.

Therefore a theoretical model for rebate contracts in the German SHI system will be developed in this paper. The model will include different types of generic producers and patient groups. Resulting from the inclusion of various types of patients, consumer preferences will play an important role in the model.

---

4 See KV Sachsen (2011)

5 See Hermann (2007)

6 See Pro Generika e.V. (2010)

7 See Carradinha (2009) and Grabowski and Mullins (1997)

The results indicate an imbalance between larger and smaller pharmaceutical producers concerning their competitive position. The strong market position of larger generic drug producers remains following the introduction of rebate contracts. However, rebate contracts are successful in intensifying competition between producers and lowering the drug expenditures of sickness funds. Crucial factors for the success of rebate contracts are mismatch costs and market access. If the mismatch costs are too high or the market access is too expensive, the contestability of the market can be reduced.

The paper is structured as follows. Section IV.2 gives an overview about the existing literature and the theoretical background influencing the development of the model approach. Section IV.3 introduces the basic model and outlines the situation before the introduction of rebate contracts. In Section IV.4 we investigate the implementation of rebate contracts under different market conditions. In Section IV.5 the results and limitations of the models are discussed with respect to the German market. Section IV.6 concludes.

IV.2 Literature review

The literature on theoretical aspects of the German SHI rebate market is very limited. Most discussions about rebate contracts are focused on aspects like medicine, entrepreneurship, law, lobbying, and politics. As they are considered in the design of the theoretical model, a short outline concerning these aspects will be given in the following.

The paper of Pruszydlo et al. (2008) discusses the medical aspects of rebate contracts. Their paper analyzes the problems of interchangeability that can occur between different generics of the same active ingredient (API). The German law only allows substitution between drugs that are identical in terms of API, strength, package size, dosage form and indication. However, drugs can still differ in shape, color, divisibility or auxiliary substances. The results of the paper indicate that these factors are relevant for convenience and compliance of the therapy. Pruszydlo et al. (2008) find that in about a third of the cases two possible

substitute drugs in the German SHI market differ in one of the factors mentioned. The problem is aggravated by rebate contracts, as only one product is eligible. Therefore, problems with drug compliance due to rebate contracts are possible.

The discussion about legal aspects of rebate contracts refers primarily to the regulation of the corresponding tendering process. The main question is whether sickness funds are companies, an opinion represented by Badtke (2007) among others, or corporations under public law, as argued by Natz (2008). In case, sickness funds are considered as private companies, they would fall under the anti-trust laws. This would limit the possibilities of sickness funds to create buying syndicates. In opposite, if they were considered as corporations under public law, they would need to tender rebate contracts and need to consider specifications about the promotion of medium-sized businesses.

As a result of the rising popularity of rebate contracts, pharmaceutical firms have to adjust their business strategies to remain competitive. Especially the shifting of the target group of decision makers from physicians to sickness funds leads to new challenges for the pharmaceutical producers. As Zeiner (2008a, 2008b, 2008c) shows, producers of patent drugs try to intensify their relationship with sickness funds by not only offering medical products but also additional health services to the members of a sickness fund. These additional services can also be part of rebate contracts.

In addition, pharmaceutical producers also express their fear of market cannibalization as companies are excluded from large parts of the market, if they lose a tender.[8] For pharmacists rebate contracts can be a reason for higher costs, since the number of different drugs that needs to be stored might increase.[9]

The existing literature on rebate contracts helps us to understand the market environment and the affected parties. However, the development of the theoretical

[8] See Pro Generika e.V. (2010)

[9] See Bauer (2008), p. 350

model was inspired by the existing literature on another popular regulatory instrument, namely reference pricing (RP).

Even though RP leads to another type of competition, we used some aspects of the theoretical discussion for our model approach. Zweifel und Crivelli (1996) model the introduction of reference prices in Germany in a Bertrand duopoly setting. In their model, they distinguish between two types of physicians that have different preferences for the original and the generic drug. Their results show that the producer of the original drug can charge a higher price than the generic drug producer after reference prices were introduced.

Cabrales (2003) uses a setting with vertically differentiated products that are chosen by the companies. The results indicate that the introduction of reference prices does not always work against the interest of the firms, as it can release the firms of the necessity to compete in quality.

Merino-Castelló (2003) develops a model with two horizontally differentiated firms that decide about quality and price of their products. One firm produces the branded original drug, the other one the generic version. Merino-Castelló uses scenarios of Bertrand and Stackelberg competition to show that reference pricing is not sufficient to increase the market share of generics. However, the results show that the market entry of generics is a credible threat and forces the brand producer to reduce prices.

Mestre-Ferrándiz (2003) models the introduction of reference prices in Spain. In a duopoly of two horizontally differentiated firms, the effect of the policy changes from drug related co-payments to a reference price scheme are analyzed. Due to the design of the Spanish reference price scheme, the price of the original drug is always located above the reference price while that of the generic drug is always below. The results indicate that a reference price scheme can lead to lower prices than a co-payment scheme.

Miraldo (2005) examines the possiblity of collusive behaviour of pharmaceutical companies in the case of reference pricing. In her model, drug producers, both horizontally and vertically differentiated, can determine ex ante the reference

price by their own pricing policy. Following this, it is possible for the producers to collude in their price setting, even without direct cooperation by taking the reference price as a focal point. In Miraldo's model, reference prices are not able to decrease prices to a lower level than without the reference pricing.

Brekke et al. (2007) develop a model with horizontal and vertical differentiation of products. In their approach, competition exists between a producer of an original (off-patent) drug, a generic drug producer, and a third firm that offers a therapeutically comparable but patent protected drug. The authors show that therapeutic reference pricing, including comparable active ingredients in a joint reference price group, increases competition but also discourages innovations to enter the market.

While our paper is inspired by the presented papers on reference pricing, we also incorporated a theoretical approach by Grilo et al. (2001). While the paper analyzes a different topic, the consumer behavior related to external factors of conformity and vanity, the presented spatial duopol model for consumer behavior can be used in our context. In their model, two shopping stores, that are horizontally differenated by their location, sell a homogenous product. The consumers are located on an interval between zero and one, however the possible position of the shops is not limited to this interval. If the position of one store was outside this range and prices were equal, it would lose the market. Hence, horizontal and vertical differentiation are incorporated in a single modelling approach.

In the spirit of Grilo et al. (2001), a horizontally and vertically differentiated Bertrand duopoly model will be used. In our model, decisions about costs and qualities are already made, therefore the firms compete only in price. The differentiation of the firms represent their position relative to the preferences of patients or sickness funds (horizontal differentiation), but also (biased) expectations about the characteristics of the products (vertical differentiation). In contrast to the other authors mentioned, we expand the market by introducing a second group of patients (respectively sickness funds) that are only price

sensitive. Further details about the market setting will be discussed in the next section.

IV.3 The Basic Model

In this section, a simple model for the demand of generic drugs in the SHI market will be developed. The basic model provides the basis for the theoretical modeling of rebate contracts in the later part of this paper.

We assume the existence of a therapeutic market for an active ingredient that is only available on medical prescription only. The market is dominated by generic drugs, while the product of the original producer - whose patent has expired - is not relevant in terms of sales.

The consumers (patients) are heterogeneous in their demand behavior. Thus, the demand for the active ingredient can be separated into two markets.

- Market I is characterized by *biased consumers* who prefer one of the two products. The price is not the only criterion for their decision between the two products.
- Market II captures the *unbiased consumers* who only react to the price of the products. Patients on this market will always choose the product that offers the lower price

There are two producers A and B each offering a single product on both markets. For type I consumers, the products are differentiated in a horizontal-vertical fashion as follows:

- Firm A produces a branded generic drug that is well known by both physicians and patients. The popularity of the drug allows the producer to charge higher prices without losing its complete demand.
- Firm B produces a no-name generic drug. The only advantage of the no-name generic drug compared to the product of manufacturer A can be its lower price.

For both markets, the demand of a consumer is assumed to be one product per period. For purpose of simplicity, we assume that the production costs are zero for both firms. This seems a reasonable assumption as marginal costs are negligible in the case of pharmaceuticals.[10] In addition, as both firms are established in the market, fix costs are considered to be sunk.

IV.3.1 The market of the biased consumers (market I)

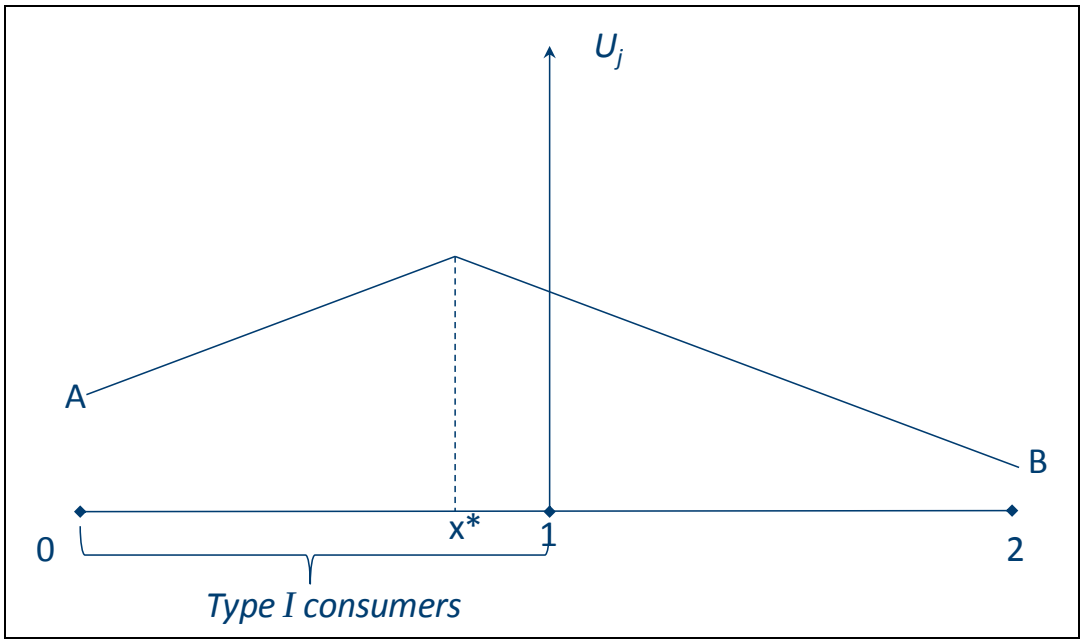
For consumers in market I the generic drugs of Firms *A* and *B* are differentiated products. Although considered as equal under therapeutic aspects, they are perceived differently by the consumers due to subjective factors. Such aspects are the popularity of the producers, the shape of a tablet or its color. Also, preferences of physicians can influence the perception of the patient for specific drugs.

To express the diversity of the consumer we use a Hotelling's location model and define the market similar to Grilo et al. (2001). As shown in Figure 2, the length of market I is assumed to be 2. Firm *A* is located at 0, while Firm *B* is located at 2. The consumers of market I are distributed uniformly on the segment [0,1]. The total mass of consumers in market I is assumed to be 1.

If a product differs in its characteristics from the position of a consumer, the deviance creates costs for the patient. These mismatch-costs are described by the factor $t > 0$, expressing the marginal loss in utility for every unit of difference between the position of the consumer and the location of the demanded product. As Figure 2 shows, all consumers would prefer the product of Firm *A*, if prices of the two products were identical. Thus, our model for the market of the biased consumers (market I) displays a combination of both vertical and horizontal product differentiation.

[10] See Schweitzer (2006), p. 144

Figure 2: The market for the biased consumers



The total utility U of the consumer $x \in [0,1]$ is

$$U = \begin{cases} u - tx - p_A & \text{if consuming product of Firm A} \\ u - t|x - 2| - p_B & \text{if consuming product of Firm B} \end{cases} \quad (1)$$

where u is the utility of the plain medical benefit of the active ingredient for consumers and p_A respectively p_B are the prices charged by the manufacturers.[11]

Excursus: Reason for the market position of Firm *B*

This excursus gives a variety of explanations for the differences in preferences by type I consumers. Except for the consumer on position $x = 1$, all consumers have a stronger preference for the product of Firm A than for the drug produced by Firm B. Consequently, in case of identical prices the consumers would always choose product A. However, from a clinical point of view, the products A and B are homogenous goods. Therefore, the difference arises from subjective factors. Possible explanations are:

[11] We assume that u is high enough so that every patient will have a positive utility from buying one of the products.

1. The separation between national pharmaceutical markets is relatively strong. Correspondingly, a firm that has its origins in the local market can establish a national image, which cannot be achieved by a foreign firm.
2. The effectiveness of a medical product also depends on the placebo effect. A lower confidence in Firm B and its product can reduce the healing effect, leading to a weaker market position of B.
3. Consumers might have gained a wider knowledge about Firm A due to other products. This leads to stronger confidence for product A.
4. Physicians, whose opinion might be biased because of advertising of Firm A, can influence the preferences of patients for the products.

IV.3.2 The market of the unbiased consumers (market II)

The second group of consumers that are included in the model (type II) are indifferent between the two generic products. Therefore, their consumption decision is solely based on the price p_i $(i = A, B)$ and their "medical need" for the product expressed in value terms. Thus, if $p_i > \min\{p_A . p_B\}$, type II consumers will not buy products from firm i. Moreover, if the medical need, denoted by $y \in [0,1]$, is lower than $\min\{p_A . p_B\}$, the consumer or physician will choose an alternative therapy option, including self-treatment or no treatment at all. The medical need of the patient, described by y, is assumed to be uniformly distributed between 0 and 1. Similar to market I, we assume that each patient only consumes a singular product i per period. The total mass of consumers in market II is assumed to be unity.[12]

We can describe the utility U of a type II consumer as:

$$U = 1 - \mathrm{y} - \mathrm{p_i} \qquad (2)$$

A consumer will buy the product if $U \geq 0$. It follows that the demand function in market II is:

[12] Therefore, the total mass of consumers in the model (type I and II) is two.

$$D^{II}(p_{min}) = 1 - p_{min} \tag{3}$$

with $p_{min} = \min\{p_A, p_B\}$. If $p_A = p_B$, it is assumed that the firms will share the market on equal terms.

IV.3.3 Benchmarks: Market equilibria without rebate contracts

In a first step we investigate the *open market* and derive the market prices for the separate markets I and II, as well as the joint market without rebate contracts. If the firms were able to separate the different type of consumers, they could apply price discrimination and charge an individual price for each market. This will be shown in the following.

IV.3.3.1 Equilibrium in the market for biased consumers (market I)

For the indifferent consumer x^* the utility from consuming product A is equal to the utility gained from product B, i.e. $U(x^*, p_A) = U(x^*, p_B)$. The equation is fulfilled for:

$$x^* = \frac{p_B - p_A + 2t}{2t} \tag{4}$$

As defined in Section IV.3.1, the consumers are located between zero and one. However, in case of $p_A \leq p_B$, the position of the indifferent consumer would be larger than one. Therefore, we can derive the following demand functions for market I:

$$\begin{aligned} D_A^I &= \min(x^*, 1) \\ D_B^I &= 1 - D_A^I \end{aligned} \tag{5}$$

and in consequence the profit functions of the manufactures (recalling that cost are supposed to be zero) are

$$\pi_A = p_A D_A^I \tag{6}$$

$$\pi_B = p_B(1 - D_A^I) \tag{7}$$

Based on this, we can formulate the following lemma.

Lemma 1: If $p_A \leq p_B$ Firm B will never gain any of the biased consumers.

The firms will choose a price that maximizes their profits given the price of their opponent. This leads to following equilibrium prices and profits:

$$p_A = \frac{4t}{3}, p_B = \frac{2t}{3} \tag{8}$$

$$\pi_A = \frac{8t}{9}, \pi_B = \frac{2t}{9} \tag{9}$$

The indifferent consumer is located on $x^* = \frac{2}{3}$, irrespective of the mismatch costs t. Correspondingly the demand for Firm A is $D_A^I = \frac{2}{3}$ and the demand for Firm B is $D_B^I = \frac{1}{3}$ in the equilibrium.

The prices and profits are increasing in t and for all $t > 0$ it holds that $p_A = 2p_B > 0$ and $\pi_A = 4\pi_B > 0$.

The higher price of the product A results from the higher preferences of consumers for product A, compared to product B. Hence, the consumers accept a higher price.

IV.3.3.2 Equilibrium in the market of the unbiased consumers (market *II*)

Based on the demand function in equation (3) the two firms face three possible outcomes concerning their profits:

$$\pi_i = \begin{cases} p_i - p_i^2 & \text{if} \quad p_i < p_j \ (i \neq j) \\ \frac{1}{2}(p_i - p_i^2) & \text{if} \quad p_i = p_j \ (i \neq j) \\ 0 & \text{if} \quad p_i > p_j \ (i \neq j) \end{cases} \tag{10}$$

This is a classic Bertrand competition. Consequently, the equilibrium price for the firms are $\mathrm{p_A} = \mathrm{p_B} = \mathrm{MC} = 0$. Since prices are identical, each firm will receive half of the demand, but profits are zero.

IV.3.4 Equilibrium in the combined market

In contrast to most other European countries, manufacturers in the German SHI market can set their sales prices for prescription drugs without restrictions. However, unless a rebate contract has been signed, they are bound to their official sales price. Also, the margins for pharmacists and wholesalers are set by legal regulations.[13] Therefore, only one nationwide market price exists for a prescription drug.

Given these regulations, we have to show how Firms A and B act when each of them has to charge the same price to all of their consumers. In the case of separated markets, equilibria in pure strategies have been found. This result does not necessarily hold for the combined market.

If the mismatch costs t are low, we have an equilibrium in pure strategies. We find, that $t^m = \frac{3}{16}\left(1+\sqrt{17}\right) \approx 0{,}96$ are the minimum mismatch costs for an equilibrium in pure strategies to exist. This leads to our first proposition.

Proposition 1

If $t \geq t^m$, a unique Nash equilibrium in pure strategies with $\mathrm{p_A} > \mathrm{p_B}$ exists. In this equilibrium, Firm A serves most of the biased consumers. Firm B supplies only a small fraction of market I, and all unbiased consumers in market II. In the case of $t < t^m$ no equilibrium in pure strategies exists.

Proof of Proposition 1

Consider $p_A > p_B$. Following equation (3), Firm B receives the whole demand on market II. Moreover, $p_A > p_B$ implies that the profit functions of the firms are:

$$\pi_A = p_A D_A^I \tag{11}$$

$$\pi_B = p_B\left(1 - D_A^I + (1 - p_B)\right) \tag{12}$$

[13] In case of over-the-counter pharmaceuticals (OTCs), pricing and margins are free. The price legislation does not apply for hospital pharmacies either.

Consequently the reaction functions lead to the following equilibrium prices and profits that are denoted by bars:

$$\bar{p}_A = t + \frac{3t}{3+8t} \tag{13}$$

$$\bar{p}_B = \frac{6t}{3+8t} \tag{14}$$

$$\bar{\pi}_A = \frac{2t(3-4t)^2}{(3+8t)^2} \tag{15}$$

$$\bar{\pi}_B = \frac{18t(1+2t)}{(3+8t)^2} \tag{16}$$

The indifferent consumer x^* of market I is located at:

$$x^*(\bar{p}_A, \bar{p}_B) = \frac{3+4t}{3+8t} \tag{17}$$

The initial condition $\bar{p}_A > \bar{p}_B$ is satisfied for all $t > 0$.

To prove the existence of a Nash equilibrium with the prices $\bar{p}_A$ and $\bar{p}_B$, it has to be shown that the firms have no incentive to deviate from the expected equilibrium prices.

We find that if Firm B sets a price $p_B \geq \bar{p}_A$, it would lose the whole market of unbiased consumers (type II) respectively half of it if $p_B = \bar{p}_A$. Also, following Lemma 1, B would also lose its market share in market I. Therefore, Firm B never has an incentive to deviate from $\bar{p}_B$.

In case of Firm A, the situation is different. In the above equilibrium candidate, Firm A relinquishes the competition market II. However, it is possible that Firm A can raise its profits by underbidding the price of Firm B.

Firm A prefers to underbid Firm B if:

$$\bar{\pi}_A < \bar{p}_B \left(\underbrace{1}_{\text{Market } I} + \underbrace{1-\bar{p}_B}_{\text{Market } II} \right) \tag{18}$$

The right hand side of equation (18) is the profit of Firm A with a price that is infinitesimal lower than the price of Firm B: Firm A will then receive the whole market I (see Lemma 1) and in addition it gets the complete market II.

Solving equation (18) for *t* leads to:

$$t < \frac{3}{16}\left(1 + \sqrt{17}\right) = t^m \tag{19}$$

Thus, we have shown that for $t > t^m$, our equilibrium candidate is indeed an equilibrium. However, for $t < t^m$ Firm A has an incentive to lower its price below the price of Firm B. In reaction to the price reduction of Firm A, Firm B will also decrease its price. Consequently, the firms will start a process of underbidding. However, they will not reach a price level that equals the marginal cost, as at one point in the underbidding process, Firm A will gain higher profits by withdrawing from market II. The reason is that even for $p_B \to 0$, Firm A can make strictly positive profits in market I by setting a strictly positive price, whereas for $p_A \to 0$ its profits would vanish.

In the Nash equilibrium for $t \geq t^m$, Firm A serves only the biased consumers in market I and has no share in market II. With rising mismatch costs t, the market share of Firm A in market I falls to $\frac{1}{2}$ as $\lim_{t\to\infty} x^* = \frac{1}{2}$.

Correspondingly, Firm B receives a higher market share in market I as t increases. Note that for $t > \frac{3}{4}$ the price $\bar{p}_B$ is higher than $\frac{1}{2}$, which is the optimal price of the market II in a monopolistic setting.

IV.4 Introduction of rebate contracts

Section IV.3 described the characteristics of the markets where in Section IV.3.3 the equilibrium prices in the separate markets as well as the joint market were derived. As stated in Section IV.3.4, German laws do not allow different prices for the same prescription drug in the pharmaceutical market. Therefore, the

equilibrium prices $\bar{p}_A$ and $\bar{p}_B$ are assumed to be the list prices of the product. They are assumed to be constant in the following.

The rebate prices of the firms are assumed to be a percentage r_i of the list prices $\bar{p}_i$ $(i = (A, B))$. For example, $r_i = 0.8$ denotes a rebate of 20 % by firm i concluding the rebate contract. We will refer to r_i as the *rebate element* in the following. Note that a higher rebate element means that a lower rebate is granted. In conclusion, the actual price paid by the sickness fund under a rebate contract is $r_i \bar{p}_i$.

The assumption of stable list prices in the following is not implausible. If we assume that the proportion between biased and unbiased consumers remains the same as in the case of the absence of rebate contracts, the list prices of the firms do not change. However, we assume that it is not possible or optimal for the firms to withdraw their products from the open market.

The introduction of rebate contracts creates new options for the firms. By closing a rebate contract with a sickness fund, the firm gains market exclusivity for this sickness fund's patients. Therefore, patients of the sickness fund receive products for which the sickness fund has a rebate contract.

Rebate contracts also change the demand side of the markets. Instead of patients, sickness funds are now assumed to represent the demand for prescription drugs. Assuming that sickness funds act as perfect agents of their members, we find that they are either preference orientated or price driven. Sickness fund I is assumed to be a representative of the biased consumers. In opposite, Sickness fund II represents the interests of the unbiased consumers.

Section IV.4.1 will describe the scenario for an active ingredient based rebate contract (*API contract*), where sickness funds issue a tender for the supply of their members with a specific active ingredient. Both Firms A and B can offer a contract for their respective products. Based on these offers, the sickness funds select the firm that offers the highest consumer surplus for their members.

Section IV.4.2 will expand the model and alter the characteristics of Firm A. Following this, Firm A will have the opportunity to give a rebate not only for a singular product but for its whole product portfolio, consisting of different active ingredients (*Portfolio contract*).

Due to the results of Section IV.3.4, the analysis is confirmed for the case $t \geq t^m$, since only under this condition an equilibrium in pure strategies exists in the open market.

IV.4.1 Active ingredient based rebate contracts

IV.4.1.1 Scenario 1a: Sickness fund I issues invitations to tender for an active ingredient (API) based rebate contract

As noted before, Sickness fund I represents the group of biased consumers. Since sickness funds act as perfect agents of their members, I will only accept a rebate agreement if it offers an equal or higher utility for its members compared to the utility without a rebate contract.

Therefore Firm A has to offer a price $r_A\bar{p}_A$ that fulfills:

$$\int_0^1 (u - tx - r_A\bar{p}_A)\,dx \geq \int_0^{x^*} (u - tx - \bar{p}_A)\,dx + \int_{x^*}^1 (u - t(2-x) - \bar{p}_B)\,dx \tag{20}$$

Similar, the condition for Firm B is:

$$\int_0^1 (u - t(2-x) - r_B\bar{p}_B)\,dx \geq \int_0^{x^*} (u - tx - \bar{p}_A)\,dx + \int_{x^*}^1 (u - t(2-x) - \bar{p}_B)\,dx \tag{21}$$

The right hand sides of the equations are identical, they express the cumulative utility of patients of Sickness fund I without rebate contract. The patients located between zero and x^* consume drug A. Patients between x^* and one consume drug B. The left sides of the conditions (20) and (21) represent the cumulated

utility for all consumers under consideration of the offered rebate contracts of Firms A respectively B. Following the conclusion of a rebate contract, all members of Sickness fund I will either use drug A or drug B.

The following Proposition 2 describes the equilibrium in the market of type I with rebate contracts. We define the critical value for t, where we observe a switch in the rebate regime as:

$$\tilde{t} = \frac{3}{4}\left(1 + \sqrt{2}\right) \approx 1.81 \tag{22}$$

As $\tilde{t} > t^m$, both $t < \tilde{t}$ and $t > \tilde{t}$ are possible, given the assumption that $t \geq t^m$.

The equilibrium values of the rebate element r_A of Firm A in the different rebate regimes are denoted as:

$$\tilde{r}_A = \frac{9 + 36t + 24t^2}{9 + 36t + 32t^2}$$
$$\hat{r}_A = \frac{3 + 8t}{6 + 8t} \tag{23}$$

Note that $\tilde{r}_A < \hat{r}_A$ for all $t > \tilde{t}$ and $\tilde{r}_A \geq \hat{r}_A$ for all $t^m \leq t \leq \tilde{t}$.

Proposition 2

In case of an active ingredient based rebate contract (API contract), in equilibrium, Firm A offers a rebate element $\hat{r}_A$ if $t \leq \tilde{t}$ and a rebate element $\tilde{r}_A$ if $t > \tilde{t}$. In both cases Firm A will gain positive profits. Firm B offers a rebate of 100 % ($r_B = 0$). However, this rebate is not sufficient to make Sickness fund I choose Firm B compared to a contract with Firm A.

Proof of Proposition 2

Let $\tilde{r}_A$ and $\tilde{r}_B$ denote rebate elements of Firm A and B that just match the conditions in (20) respectively (21) with equality:

$$\tilde{r}_A = \frac{9 + 36t + 24t^2}{9 + 36t + 32t^2} \tag{24}$$

$$\tilde{r}_B = \frac{3(3+8t) - 2t^2}{6(3+8t)} \tag{25}$$

These two critical values are decreasing in t for all $t > t^m$. Also, it holds that $\tilde{r}_A - \tilde{r}_B > 0$ for all $t \geq t^m$. Therefore Firm B always has to offer a lower rebate element (meaning a higher rebate) than Firm A to compensate the higher mismatch costs of the patients.

While the rebate element of Firm A is always greater than zero with $\lim_{t\to\infty} \tilde{r}_A = \frac{3}{4}$, Firm B would need to offer a negative rebate element for $t > \frac{3}{4}\left(1+\sqrt{2}\right) = \tilde{t}$. In this case, Firm B would incur a loss with a rebate contract and would refuse to compete in the tender process.

However, even though Firm B does not make an offer for a rebate contract, it can still be profitable for Firm A to conclude a rebate contract to gain market exclusivity.

Under the assumption of $t > \tilde{t}$, Firm A has to offer a rebate to Sickness fund I that fulfills equation (20) to win the tender. Following this, $\tilde{r}_A$ is the minimum and also the optimal rebate element for Firm A. A higher rebate would not expand the demand for drugs and thus only diminish profits.

As Firm A receives the whole market in case of a rebate contract, the profit is:

$$\tilde{\pi}_A = \tilde{r}_A \bar{p}_A = \frac{2t(9+36t+24t^2)}{(3+8t)^2} \tag{26}$$

It can be shown that for all $t > t^m$, it holds $\tilde{\pi}_A > \bar{\pi}_A$. Consequently, Firm A will always offer a rebate contract even if it does not compete with Firm B. The reason for the higher profit is the increase in demand for their product and the possibility of Firm A to conduct a price discrimination between Sickness fund I and II.

In the case of $t^m < t \leq \tilde{t}$ the rebate contract is profitable for both firms. If the firms offered their critical rebate elements of $\tilde{r}_A$ and $\tilde{r}_B$ respectively in the first bidding round, the sickness fund would be indifferent and both firms would have a chance of $\frac{1}{2}$ to receive the rebate contract.

However, it is obvious, that this result cannot be an equilibrium. Both firms have an incentive to deviate from $(\tilde{r}_A, \tilde{r}_B)$ as the firm offering a slightly higher rebate will receive the whole market. Consequently, the other firm will counter with a higher rebate.

Thus, a Bertrand competition emerges, in which Firm A is in a better position than Firm B, due to the preference structure of Sickness fund I. Since members of I are assumed to have a preference for product A, the net price $(r_B\bar{p}_B)$ of Firm B must be lower than the net price $(r_A\bar{p}_A)$ of Firm A.

Given Firm B would offer a rebate of 100 % $(r_B = 0)$, the reaction of Firm A can be expressed as:

$$\int_0^1 (u - tx - r_A\bar{p}_A)\, dx \geq \int_0^1 (u - t(2 - x))\, dx \tag{27}$$

The right hand side of the equation displays the utility of the consumers in case of a rebate contract with Firm B and $r_B\bar{p}_B = 0$. The left hand side is the utility for a contract with Firm A. Expression (27) leads to the critical

$$\hat{r}_A = \frac{3 + 8t}{6 + 8t} \tag{28}$$

and the profit

$$\hat{\pi}_A = \hat{r}_A\bar{p}_A = t \tag{29}$$

The rebate lies between $\frac{1}{2} \leq \hat{r}_A < 1$ and the profit $\hat{\pi}_A$ of Firm A is greater than zero. The results indicate that Firm A can outpace Firm B even if Firm B gives a 100 % rebate.

As shown in proof of scenario 1a, for $t > \tilde{t}$, Firm B would have to offer a rebate element $r_B < 0$ to win the tender. However, the maximum rebate element it will offer is $r_B = 0$, which is analogous to a rebate of 100 %. Firm A could offer a rebate element $\hat{r}_A$ to generate an equal utility for Sickness fund I. However, the sickness fund would not accept it. Firm A has to give the lower rebate element $\tilde{r}_A$ to make Sickness fund I indifferent to the open market situation.

For the case of $t \leq \tilde{t}$, Firm A faces the opposite situation. A rebate element $\tilde{r}_A$ would be sufficient to match the utility in the open market case. Yet, Firm A has to give $\hat{r}_A < \tilde{r}_A$ to outbid the offer of Firm B in this case.

IV.4.1.2 Scenario 1b: Sickness fund II issues invitations to tender for an active ingredient (API) based rebate contract

In this scenario, Sickness fund II offers an active ingredient based rebate contract. The sickness fund represents consumers whose consumption decision depends only on the price of the products.

Note that in market II the price reduction due to a rebate contract will increase the demand for the product. This means that Sickness fund II will transfer the savings of the rebate contract to the patients (in the form of lower co-payments or insurance premiums). Also, physicians will prescribe the drug more often because rebates are considered in the efficiency evaluation of their drug budgets. This implies welfare gains due to rebate contracts.

Considering this, the following Proposition 3 describes the equilibrium in the market of type II with rebate contracts.

Proposition 3

For all $t > t^m$ there exists a Nash equilibrium in pure strategies with $r_i = 0$ $(i = A, B)$ for both firms.

Proof of Proposition 3

Like sickness fund I, sickness fund II will only accept a rebate contract that offers at least the same utility for its members than in the situation without a contract.

If a rebate element r_i is granted and firm i is chosen, the consumer surplus of the sickness fund II is:

$$\int_0^{1-\bar{p}_i r_i} (1-q) - \bar{p}_i r_i \, dq \tag{30}$$

As Firm A is not present in market II before the introduction of rebate contracts due to its higher list price, it always has an incentive to offer a rebate to enter the market. Note that Firm B might also have an incentive to give a rebate. Firm B will only offer a rebate immediately, if the list price $\bar{p}_B$ is higher than the profit maximizing monopoly price $\frac{1}{2}$. This holds for all $t > \frac{3}{4}$ and as our model is limited to $t \geq t^m$ with $t^m > \frac{3}{4}$, Firm B will always offer a rebate element.

As every (reasonable) combination of strictly positive rebate element and list price will generate positive profits and increase the utility of the Sickness fund II, the firms will start a race of underbidding until they reach $r_A\bar{p}_A = r_B\bar{p}_B = MC = 0$. As a result, every firm will make zero profits and will conclude a rebate contract with Sickness fund II with a probability of $\frac{1}{2}$.

As we have seen so far, rebate contracts reduce net prices (rp). Yet, only in case of market II we reach a price equal to marginal costs and the firms have equal chances to win the contract. In contrast, on market I, Firm A keeps its advantage regarding the preferences of the consumers and will always win the bid. Thereby, the net prices on market I will not reach the level of the marginal cost.

However, API contracts are only one possible form of rebate contracts. Instead, some sickness funds do not offer tenders for a single ingredient, but for the whole product portfolio of pharmaceutical producers. This kind of contracts, called portfolio rebate contracts, will be discussed in the next section.

IV.4.2 Portfolio rebate contracts

So far, we assumed that each firm produces only one single drug. Although the majority of generic producers sells only a small number of different drugs, there are a few large firms that have a portfolio up to over 200 different active ingredients.[14]

[14] See INSIGHT Health (2009)

We now assume that Firm A is a brand name generic producer that also offers a variety of drugs besides product A. These other products are bundled as "product s" with price p_s. The combination of product s and product A forms the portfolio of Firm A. In contrast, Firm B is supposed to be a small producer that only has a single product in its portfolio. In consequence, only Firm A can offer portfolio rebate contracts to sickness funds.

On the open market the demand for the portfolio s is:

$$D^s(p_s) = 1 - p_s \tag{31}$$

We assume that $D^s(p_s)$ is the demand for the product s. If Firm A had a monopoly in the market, the price for product s would be $\frac{1}{2}$. Therefore, we assume $p_s \leq \frac{1}{2}$. Note that the maximum demand for product s is defined as one. This underlines the importance of our main products A and B compared to products represented by product s.[15]

In the following we compare the portfolio contract to the situation where the sickness funds offer a single API contract for product A or B and no contract for product s. Yet, an API contract for product s could also be possible. However, such kind of contract seems to be unlikely. There are several reasons for this assumption. In the case Firm A has a monopoly for product s, it has no incentive to offer any rebate because it will not increase its profits. If Firm A faces competition for product s, it might still not want to conclude a rebate contract for this product alone due to transaction cost. In contrast, a joint rebate contract for products A and s might save on transaction costs.

If Firm A offers a rebate contract, we assume that a rebate element r_s is chosen that is identical for product A and s. We also assume that a rebate leading to a lower net price will expand the demand for product s (similar to market II for product A).

---

[15] It is quite common that even large portfolio firms earn a major part of their overall profits from the sales of only a few products.

IV.4.2.1 Scenario 2a: Sickness fund I issues invitations to tender for portfolio rebate contracts and Firm A can offer a portfolio contract

Similar to the previous scenarios, Firm A has to offer a rebate that will make Sickness fund I at least indifferent to the situation without a contract. Therefore, Firm A must fulfill the following condition (compare condition (20)):

$$\begin{aligned}\int_0^1 (u - tx - r_s\bar{p}_A)\,dx + \int_0^{1-p_s r_s} (1-q) - r_s p_s\,dq \\ \geq \int_0^{x^*} (u - tx - \bar{p}_A)\,dx + \int_{x^*}^1 (u - t(2-x) - \bar{p}_B)\,dx \\ + \int_0^{1-p_s} (1-q) - p_s\,dq\end{aligned} \tag{32}$$

The term $\int_0^{1-p_s r_s}(1-q) - p_s r_s\,dq$ expresses the utility of the sickness fund for product s after the rebate. It can be expanded to:

$$\int_0^{1-p_s} (1-q) - p_s dq + \int_0^{1-p_s} (p_s - r_s p_s)\,dq + \int_{1-p_s}^{1-r_s p_s} (1-q) - r_s p_s dq \tag{33}$$

The first term expresses the utility of the sickness fund in the open market. The second is the utility gain through the lower price for the same quantity. The third term represents the utility gain through the higher amount of consumed products. The first term of (33) can be subtracted from both sides of condition (32) and the right side of the latter becomes identical to that of condition (20):

$$\begin{aligned}\int_0^1 (u - tx - r_s\bar{p}_A)\,dx \\ + \int_0^{1-p_s} (p_s - r_s p_s)\,dq + \int_{1-p_s}^{1-r_s p_s} (1-q) - r_s p_s dq \\ \geq \int_0^{x^*} (u - tx - \bar{p}_A)\,dx + \int_{x^*}^1 (u - t(2-x) - \bar{p}_B)\,dx\end{aligned} \tag{34}$$

Since Firm B only offers a single product, it faces the same condition (21) as in Scenario 1a.

Again there are two critical values $\tilde{r}_s$ and $\hat{r}_s$ (see equation (41) and respectively (43) in Appendix 1), with $\tilde{r}_s < \hat{r}_s$ for $t > \tilde{t}$, such that the following holds:

Proposition 4

Firm A will offer a portfolio contract with rebate element $\tilde{r}_s$ if $t > \tilde{t}$ and the rebate element $\hat{r}_S$ if $t^m \leq t \leq \tilde{t}$. In both cases Firm A will gain positive profits, even higher than under an API contract for product A and no rebate contract for product s. In contrast, Firm B cannot make a contract offer that makes sickness fund I better off compared to the portfolio contract proposal of Firm A.

Proof of Proposition 4

The critical rebate element $\tilde{r}_s$ for which (34) holds with equality can be seen in equation (43) in Appendix 1. It can be shown that $0 < \tilde{r}_s < 1$ holds for all $t > t^m$.

For Firm B the critical rebate elements remains $\tilde{r}_B$ (see equation (25). If $t > \tilde{t}$, we have shown in section IV.4.1.1, that the critical rebate element must be smaller than zero. Therefore, Firm B will not make a bid for the contract. If $t \leq \tilde{t}$, Firm B will lower its rebate element down to $r_B = 0$.

Because Firm B cannot offer a portfolio contract, Firm A has three choices. It could refrain from offering a rebate , offer an API contract for product A, or it could bargain a rebate contract for product A and product s.

The results of section IV.4.1.1 already indicated that an API rebate contract increases profits, compared to the situation without rebate contracts. Consequently, the decision is reduced to the choice between an API and a portfolio contract.

The Firm A will prefer the portfolio contract if:

$$\underbrace{(\tilde{r}_s\bar{p}_A + (1-\tilde{r}_S p_s)\tilde{r}_S p_s)}_{"portfolio\ profit"} - \underbrace{(\tilde{r}_A\bar{p}_A + (1-p_s)p_s)}_{"API\ profit"} \geq 0 \qquad (35)$$

It can be shown that the portfolio profit is always higher than the API profit for $t > \tilde{t}$ and $0 < p_s \leq \frac{1}{2}$. The reason for the higher profits is the larger consumed amount of product s. In case of the API contract for product A, Firm A can

compensate the utility loss of sickness fund I due to the switching from Firm B to Firm A, only through price reduction. With the portfolio contract, the sickness fund is also compensated by the demand expansion of the portfolio market. The results indicate a welfare increase on the market of product s. Firm A can sell product A for a higher price ($\tilde{r}_s\bar{p}_A$) and therefore overcompensate the profit loses for the remaining products of the portfolio.

For $t^m \leq t \leq \tilde{t}$ again an underbidding process between the two firms occurs, until the rebate element where Firm A can outpace Firm B.

Similar to (27) Firm A can offer a rebate that fulfills the following condition:

$$\int_0^1 (u - tx - r_s\bar{p}_A)\,dx + \int_0^{1-r_sp_s} (1-q) - r_sp_s\,dq \geq \int_0^1 (u - t(2-x))\,dx + \int_0^{1-p_s} (1-q) - p_s\,dq \tag{36}$$

The critical rebate $\hat{r}_s$ element that matches both sides is derived in equation (43) in Appendix 1.

Again Firm A makes higher profits with the portfolio contract compared to the API contract. In conclusion, Firm A will receive the whole market I, as a rebate factor $r_B = 0$ of Firm B would not lead to a higher benefit for the sickness fund.

A portfolio contract leads to higher profits for Firm A compared to an API contract or the open market. The reason is the increased demand on the market of product s. In case of an API contract Firm A can only increase the surplus of the consumers by lowering its price. It now sells more products (the ones sold before by Firm B), however the total amount of products stays the same. It can be shown that, if a price reduction on the market for product s led to no increase in demand, Firm A would be indifferent between an API contract and a portfolio contract. The profit gain due to the rebate contract for product A would be consumed by the loss for product s. With an increase in the demand the consumers are not only better off by the lower price but also more consumers are willing to buy product s.

The increase of the demand for these products overcompensates the loss due to lower prices.

IV.4.2.2 Scenario 2b: Sickness fund II issues invitations to tender for portfolio rebate contracts and Firm A can offer a portfolio contract

In this scenario Firm A can offer a portfolio contract to Sickness fund II. The sickness fund will accept that offer if the following condition is fulfilled:

$$\int_0^{1-r_s\bar{p}_A} (1-q) - r_s\bar{p}_A\, dq + \int_0^{1-r_s p_s} (1-q) - r_s p_s\, dq \geq \int_0^{1-\bar{p}_B} (1-q) - \bar{p}_B\, dq + \int_0^{1-p_s} (1-q) - p_s\, dq \tag{37}$$

This means, the accumulated utility in case of a rebate contract (left hand side of (37) must be at least as high as in the market equilibrium without a rebate contract.

As before the firms will start a competition of underbidding and condition (37) can be changed to the case were $r_B = 0$:

$$\int_0^{1-r_s\bar{p}_A} (1-q) - r_s\bar{p}_A\, dq + \int_0^{1-r_s p_s} (1-q) - r_s p_s\, dq \geq \int_0^{1} (1-q)\, dq + \int_0^{1-p_s} (1-q) - p_s\, dq \tag{38}$$

As in the results of scenario 2a the term $\int_0^{1-p_s}(1-q) - p_s\, dq$ can be separated out of expression (38). Thus, the right side expresses the prescribed consumer surplus for Sickness fund II in condition (30) for the case when $r_i = 0$.

Therefore, we can express the condition for Firm A as:

$$\int_0^{1-r_s\bar{p}_A} (1-q) - r_s\bar{p}_A \, dq + \int_0^{1-p_s} (p_s - r_s p_s) \, dq + \int_{1-p_s}^{1-r_s p_s} (1-q) - r_s p_s dq \geq \int_0^1 (1-q) \, dq \quad (39)$$

The following Proposition 5 describes the equilibrium in the market $I\!I$ if Firm A is able to offer a portfolio contract. Contrary to Proposition 3, the equilibrium value $\hat{\hat{r}}_s$ (see equation (45) in Appendix 2) of Firm A will now be greater than zero:

Proposition 5

Firm A will offer a portfolio rebate element $\hat{\hat{r}}_s > 0$ for all $t \geq t^m$ that will lead to positive profits for Firm A, even higher than in case of an API contract for product A and no rebate contract for product s. In contrast, Firm B cannot offer a rebate element $r_B \geq 0$ which generates a higher consumer surplus for Sickness fund $I\!I$ than the offer of Firm A.

Proof of Proposition 5

Similar to Section IV.4.1.2 the introduction of rebate contracts leads to an underbidding process. While Firm A can offer a portfolio rebate contract, Firm B cannot offer a comparable rebate due to the lack of a larger product portfolio.

Consequently, Firm A increases the utility for members of Sickness fund $I\!I$ and still realizes profits. Therefore, Firm A has to match condition (39). The right hand side of the equation shows the benefit of the sickness fund with a rebate offer $r_B = 0$ by Firm B. The left hand side shows the utility in case of a contract with Firm A. As a result we receive the critical rebate element $\hat{\hat{r}}_s$ of equation (45), which can be found in Appendix 2.

The rebate element $\hat{\hat{r}}_s$ lies between 0 and 1 for $t \geq t^m$ and $0 < p_s \leq \frac{1}{2}$. Firm A now gains a profit on the market for product A. Still, it has to be evaluated if the profit growth for drug A compensates the profit loss for products s. Thus, Firm A will offer the rebate $\hat{\hat{r}}_s$ if

$$\underbrace{(1-\hat{\hat{r}}_s\bar{p}_A)\hat{\hat{r}}_s\bar{p}_A + \left(1-\hat{\hat{r}}_s p_s\right)\hat{\hat{r}}_s p_s}_{profit\ of\ portfolio\ contract} \geq \underbrace{(1-p_s)p_s}_{profit\ of\ API\ contract} \qquad (40)$$

It can be shown that the left side of equation (40) is higher for all $t \geq t^m$ and $0 < p_s \leq \frac{1}{2}$. Therefore Firm A prefers the portfolio contract.

Compared to the offer by Firm ($r_B = 0$), Sickness fund $I\!I$ loses benefit on the market of product A (respectively B) if it accepts the bid of Firm A. But Firm A compensates the sickness fund with a benefit gain on the market for product s.

IV.4.3 Recapitulation of the results on rebate contracts

In the previous sections, we have shown four different scenarios for rebate contracts. Table 17 summarizes the results for each scenario. In three of them, Firm A receives the rebate contract and can increase its profits. In contrast, Firm B does not make any profit. Only in one scenario Firm B has a 50 % chance of winning the tendering process for a rebate contract, but its profits would be zero.

The sickness funds improve their utility or are, at least, indifferent. In the market of Sickness fund I the increase of total welfare depends on the mismatch cost t. In the market of Sickness fund $I\!I$ total welfare always increases, independent of the value of t (note that following Proposition 1 our solutions considerations are confined to $t \geq t^m$).

Table 17: Summary of the tendering results

	Sickness fund I	**Sickness fund II**
API contract	Firm A wins and gains higher profit than without a rebate contract.	Firm A and Firm B have a chance of 50 % to win the contract. They make no profits.
	For $t < \tilde{t}$ total utility of sickness fund increases, for $t \geq \tilde{t}$ total utility remains the same as without a rebate contract.	Sickness fund receives maximum consumer surplus of product A or B, independent of the value of t.
	Total welfare increases, if mismatch cost are high enough.	Sickness fund receives the maximum possible total welfare.
Portfolio contract	Firm A wins and gains higher profits than with API rebate contract.	Firm A wins and gains higher profits than with a API contract.
	For $t < \tilde{t}$ total utility of sickness fund increases, for $t \geq \tilde{t}$ total utility remains the same as without a rebate contract.	Sickness fund receives a surplus gain equal to to the API contract.
	Total welfare increases, if mismatch cost are high enough. In general, the total welfare is higher than under API contract due to higher profits of Firm A.	Total welfare increases, as the maximum total welfare of product A plus the former profit of Firm A for product s is shared between firm and sickness fund.

The results show that the biased consumers, represented by Sickness fund I, will always receive the product of Firm A. In contrast, the unbiased consumers represented by Sickness fund II will either receive product A or B.

Based on the results, Firm A will always prefer the portfolio contract because of the higher profits of this option. In contrast, the sickness funds are indifferent between the API and the portfolio contract. However due to the higher profits, Firm A obtains the possibility to convince the sickness funds to favor portfolio contracts by giving a slightly higher rebate.

Under these circumstances, the portfolio contract would always be the superior rebate contract option. Therefore, our analysis of the API contracts seems unnecessary. However, as we can see for the portfolio contract, Firm A would gain a monopolistic position not only for the API contract (where it is intended) but also for their remaining products consumed by the insurees of the sickness funds. In the long run this would lead to a monopolistic position for firm A in the whole SHI system. The legislature has recognized this issue and changed the legal framework for rebate contracts accordingly. Following 2009, portfolio contracts only fulfill the legal requirements for a rebate contract in very rare cases. We will discuss this in further detail in Section IV.5.

In regard to the total welfare of rebate contracts, the results are mixed. In the market of sickness fund I, the welfare gain depends on the value of the mismatch cost t. Firm B always loses its profits, independently of t. Firm A sells at a lower price but can increase its output and in sum increase its profits. The utility of the sickness fund increases when mismatch cost are low $(t \leq \tilde{t})$ and remain the same when mismatch cost are high $(t \geq \tilde{t})$. It can be seen from the profit functions (26) and (29) of Firm A that in case of the API contract profits are increasing in t. Consequently, the profit gain for Firm A, compared to the profit loss for Firm B, increases when *t* gets higher. This leads to a total welfare increase when t is larger than $\frac{3}{2}$. As we have shown in expression (40), the profits under a portfolio contract are always higher than under an API contract. Therefore, the profit gain of Firm A is even more higher relative to the profit loss of Firm B than in the case of the API contract. However, unlike for the API contract, the critical t, where the welfare increases, depends now also on price p_s of product s. If Firm A has a monopoly for product $(p_s = \frac{1}{2})$, the total welfare is larger compared to the situation without rebate contracts when $t > 1.3514$.

In case of the market of sickness fund II, the welfare effects are more intuitive. With the API contract, the actual price $r_i\bar{p}_i$ is zero. Therefore all patients with a medical need can consume the good and the sickness fund receives the maximum welfare in the market. When the model is extended to portfolio contracts, the

welfare gain is even higher than under the API contract. In the case of portfolio contracts, Firm A needs to match with its offer the same consumers surplus as under the API contract as the actual price of Firm B will be again $r_B\bar{p}_B = 0$. Therefore, the total consumer surplus is the same as under the API contract, yet Firm A can increase its profits, since the gain for product A is higher than the loss for product s.

In the following section the political implications of these results will be discussed.

IV.5 Interpretation of the results in relation to the German pharmaceutical market

In a market for generics with free price setting, it is expected that prices are close to the marginal cost of production, as generic drugs are goods whose substitutability and (therapeutic and pharmacologic) homogeneity are the preconditions for market entry. But the need for regulatory instruments like reference pricing and the Aut-Idem rule[16] show that the market prices are usually above marginal costs. In reaction to reference pricing the firms are forced to lower their prices. Also, the Aut-Idem rule intensifies the price competition between the different producers. But even then the firms have still the possibility to grant rebates in case of a rebate contract.

Hotelling's location model was used to explain the price differences between the various brands of a generic drug. The model was helpful to explain why the occurring prices lie above marginal costs by assuming the existence of subjective preferences of both patients and physicians for specific generic drugs.

---

[16] Aut-Idem (latin: or the same) rule in Germany: As long as the physician has not explicitly excluded "Aut-Idem" on the receipt, the choice of the pharmacist is limited to the three cheapest drugs with the same active ingredient, package size, strength, application form and indication. If the physician has stated a specific drug on the receipt and not just the nonproprietary name (INN), the pharmacist may also dispense the drug on the receipt. When there is a rebate contract and Aut-Idem is not excluded by the physician, the pharmacist has to dispense the rebated drug (see Spitzenverband Bund der Krankenkassen (2009)

As mentioned in the introduction, experts are divided between two different opinions how rebate contracts could change the market of the SHI system. One group expects an increase of competition and lower prices due to rebate contracts. The other fraction fears a squeeze out of small producers and therefore, in the long run, higher prices due to an oligopolistic or monopolistic market situation.

Our results show that both sides have reasonable arguments for their position. Our model predicts lower reimbursement prices for the sickness funds but also the tendency for monopolization. Of course, our model is only a simplification of the existing forms of contracts. In particular, we assume that firms just grant a simple rebate on the price of a drug. In reality, the German law allows far more complex rebate contracts. For example, firms are allowed to close contracts that include a general rebate on the price and an additional rebate for the increased amount of demand they generated due to the rebate contract. However, this does not alter the general requirement that the firms have to generate at least the same consumer surplus for the sickness funds as without a rebate contract. However, this condition again favors the bigger firms, as they can make better comprehensive offers. As a result, smaller producers could be discouraged to operate in the market.

In concern to the negative aspects of rebate contracts, we found that especially portfolio contracts reduce the chances for small producers. This danger was already acknowledged by the legal institutions in Germany. Since a 2009 court decision, sickness funds are considered as corporations under public law and therefore are obliged to tender Europe-wide.[17] Also they have to divide the contract in lots to make it easier for medium-sized businesses to participate in the tender. Consequently, the German Federal Social Insurance Authority prohibits portfolio contracts and appeals to the sickness funds to re-tender their rebate contracts.[18] Based on the court decision and the opinion of the German Federal Social Insurance Authority, the legislator concretized the Book V of the Social

[17] See Court of Justice of the European Communities (2009)

[18] See Plate (2009)

Code at the beginning of 2011. The duration of a contract should be two years. The variety of providers shall be taken into consideration. Our results indicate that these legal changes are reasonable.

While the legislator wants to avoid a declining number of producers in the market, a decrease in competition does not necessarily need to occur. Currently there are at least three pharmaceutical companies in Germany that correspond to the Firm A in our model (large portfolio and seen as a brand producer by consumers). With the introduction of rebate contracts, the firms would either underbid themselves to a rebate of 100 % or we might see a persistence of high prices (including rebate) when the German patients have a high preference (high mismatch cost) for specific branded generics.

A relatively high number of unbiased consumers could lower the power of the branded generics producers, because it gets more unattractive to give up the demand of the unbiased consumers in favor of higher prices charged to the biased consumers. However, they can use rebate contracts on the market of the unbiased consumers to improve their general market position. Before the rebate contract, only non-branded generic producers of type B supplied the consumers on the market. With the API contract firms of type A will still not make profits but neither will the former incumbent. Thereby branded generic producers can make it unattractive for small firms to compete on the German SHI drug market. If the brand firms can generate positive profits on other markets of their portfolio, they might even accept losses on markets of unbiased consumers in the short run to drive small competitors out of the market. Hence, the market access for new firms is an import aspect for contestability of the generic market. As Natz (2008) points out, the existence of rebate contracts allows foreign pharmaceutical producers to enter the German market more easily, as they can focus their key account management on the sickness funds and not the heterogeneous mass of physicians. Therefore, even with no local firms of type B in the market, small foreign producers can be a continuous threat for the established market participants.

Another possible strategy for brand firms could be collusive agreements concerning rebate contracts. The larger, established firms in the market could agree that for every sickness fund only one of them offers a rebate. The result would depend on the number of repeated games (frequency of tenders, number of sickness funds), the potential of the firms to threat the (possible) competitors in the market, and the duration of a rebate contract. A deeper analysis is beyond the focus of this paper but it seems reasonable to expect that the options to collude diminish as market entry for new competitors becomes cheaper and the duration of a rebate contract decreases.

Reference pricing, which is an important aspect of the German generic market, was not addressed in this paper. Reference prices foremost influence the price setting on the open market. The German reference prices are based on the existing sales prices in the market and have to take into account that a minimum amount of different drugs is available for the intended reference price.[19] In our model, reference prices would set a maximum price for Firm A or a kink in the demand for product A. However, it would not change the general advantage of Firm A to set a higher price than Firm B. In addition, for the case of a rebate contract the reference price does not play a role, as rebates are not considered in the calculation of the reference prices.

When we compare the results of the theoretical literature on reference pricing with our results, we find that the German rebate contracts are a radical regulation instrument. It exerts a stronger pressure on prices than reference pricing, but it cannot level out the differences in market power between the firms.

The analysis of the rebate contracts left out cases where the mismatch cost are $0 < t < t^m$. The reason is the non-existence of a stable list price $\bar{p}_i$ in the combined market without rebate contracts. A deeper analysis of this interval would have distracted from the intrinsic idea of this paper to show the interaction between the firms and the sickness funds in the rebate market. However, it should

[19] For further details about the calculation of the German reference prices see Schumacher and Greiner (2008) and Stargardt et al. (2005)

be noted that rebate contracts, if they are possible for values of t smaller than t^m, might stop the occurring circle of price decreases and increases, as with the existence of a rebate contract, changes in list price will not help to regain market share.

IV.6 Conclusion

Rebate contracts are a relatively new concept in the German market. Policy makers were immediately confronted with demands by the pharmaceutical industry to repeal them. Primarily installed to reduce the expenditures of the sickness funds, rebate contracts are able, under specific circumstances, to reduce the level of reimbursement of drugs to the level of marginal drug cost. However, in most cases a price markup will remain, because large and preferred producers can outperform smaller competitors before marginal costs are reached. Hence, rebate contracts bear the danger that smaller competitors are excluded from the market, leading to market concentration. Yet, it is questionable, whether these arguments are sufficient enough to withdraw the legislation for rebate contracts. But the legislator reacted with more specific frameworks and virtually forbid portfolio contracts.

The results of the paper indicate that the effects of rebate contracts depend on the market framework. By setting the proper regulatory framework, rebate contracts can lead to savings and avoid monopolistic market positions.

First, to prevent the negative aspects of rebate contracts, the contestability of a market has to be sustained. This can be difficult because the rebate contracts diminish the incentives of pharmaceutical companies to produce drugs when they do not participate in any of these contracts.

Second, only single active-ingredient contracts should be allowed. With portfolio contracts, smaller producers are heavily disadvantaged as they cannot compete with the diversity of the larger firms.

Third, the duration of a contract should not be too long, otherwise the excluded firms will most likely leave the market and new competitors cannot enter. The

renegotiation of the contracts gives an incentive to remain in the market and the sickness fund might anticipate cost savings in the productions process through higher rebates.

Finally, also the demand side should be examined. It should be observed if the decreasing number of sickness funds, primary due to a number of mergers and the creation of buying syndicates by smaller sickness funds lead to oligopolistic structures on the demand side. However, as sickness funds are bound to regulations for governmental authorities the possible risks for a gross distortion of the pharmaceutical market should be small. It is also questionable whether one producer would have the capacity to supply medicines to about 70 million insurees in the SHI system.

In conclusion, we find that the rebate contracts have a great potential for savings, but possibly not to the expected extent. A sufficient framework is needed to unfold the potential. The market is still under development and in upcoming years, an empirical evaluation of the market is needed to show how the market picture is affected by this new regulatory instrument.

IV.7 Appendix

IV.7.1 Appendix 1

Rebate elements in Scenario 2a

In Section IV.4.2.1 we describe the Scenario 2a: Sickness fund I issues invitations to tender for portfolio rebate contracts and Firm A has the possibility to offer a portfolio contract. The rebate offer of Firm A depends on the possibility of Firm B to offer a rebate as well. For $t \leq \tilde{t}$ Firm B will submit a rebate element $r_B = 0$, but for $t > \tilde{t}$ Firm B could satisfy the condition in equation (21) only with a rebate element $r_B < 0$, therefore it will not participate in the tender. As a result the are at least two different outcomes for the rebate element r_s of Firm A.

In case of $t > \tilde{t}$, the rebate element r_s of Firm A has to satisfy the condition (34). Solving that condition at equality leads to two solutions:

$$r_s^1 = \frac{p_s+t+\frac{3t}{3+8t}-\sqrt{\frac{4t^2(3+4t)^2+4p_st(3+4t)(3+8t)-2p_s^3(3+8t)^2+p_s^4(3+8t)^2+p_s^2\left(9-4t\left(-3+4t(5+6t)\right)\right)}{(3+8t)^2}}}{p_s^2} \quad (41)$$

and

$$r_s^2 = \frac{p_s+t+\frac{3t}{3+8t}+\sqrt{\frac{4t^2(3+4t)^2+4p_st(3+4t)(3+8t)-2p_s^3(3+8t)^2+p_s^4(3+8t)^2+p_s^2\left(9-4t\left(-3+4t(5+6t)\right)\right)}{(3+8t)^2}}}{p_s^2} \quad (42)$$

But only r_s^1 satisfies the conditions of our model that $0 \leq r_s < 1$ for all $t \geq t^m$ and $0 < p_s \leq \frac{1}{2}$. Therefore r_s^1 is the only feasible solution and we define it as our critical value: $\tilde{r}_s = r_s^1$.

For $t \leq \tilde{t}$, the rebate element $r_s$of Firm A has to satisfy the condition in equation (36). There are two solutions for r_s that satisfy the condition:

$$r_s^3 = \frac{p_s+t+\frac{3t}{3+8t}-\sqrt{p_s^4-2p_s^3-2p_s^2(t-1)+2p_s\left(t+\frac{3t}{3+8t}\right)+\left(t+\frac{3t}{3+8t}\right)^2}}{p_s^2} \quad (43)$$

and

$$r_s^4 = \frac{p_s+t+\frac{3t}{3+8t}+\sqrt{p_s^4-2p_s^3-2p_s^2(t-1)+2p_s\left(t+\frac{3t}{3+8t}\right)+\left(t+\frac{3t}{3+8t}\right)^2}}{p_s^2} \quad (44)$$

As before only one of the solutions satisfies the conditions of our model. Here it is r_s^3 and we define it as the critical value, $\hat{r}_s = r_s^3$.

IV.7.2 Appendix 2

Rebate elements in Scenario 2b

In section IV.4.2.2 we describe the Scenario 2b: Sickness fund II issues invitations to tender for portfolio rebate contracts and Firm A has the possibility to offer a portfolio contract. The rebate offer of Firm A depends on the offer of Firm B. The two firms are in a race of underbidding. Due to its portfolio, Firm A has the advantage to outrun Firm B and still make profits. Hence, Firm A needs to satisfy the conditions about the consumers surplus of Sickness fund II in

expression (39), where Firm B offers a rebate of 100 % ($r_B = 0$). Solving at equality gives two solutions:

$$r_s^5 = \frac{p_s + t + \frac{3t}{3+8t} - \sqrt{\left(p_s + t + \frac{3t}{3+8t}\right)^2 + p_s(p_s - 2)\left(p_s^2 + \left(t + \frac{3t}{3+8t}\right)^2\right)}}{p_s^2 + \left(t + \frac{3t}{3+8t}\right)^2} \tag{45}$$

and

$$r_s^6 = \frac{p_s + t + \frac{3t}{3+8t} + \sqrt{\left(p_s + t + \frac{3t}{3+8t}\right)^2 + p_s(p_s - 2)\left(p_s^2 + \left(t + \frac{3t}{3+8t}\right)^2\right)}}{p_s^2 + \left(t + \frac{3t}{3+8t}\right)^2} \tag{46}$$

The condition $0 \leq r_s^5 < 1$ holds for all $t \geq t^m$ and $0 < p_s \leq \frac{1}{2}$. In case of r_s^6 the condition is only fulfilled for $t \geq \frac{1}{8}\left(5 + \sqrt{73}\right) \approx 1.69$. In consequence, Firm A could choose between two possible rebate elements in this case. But naturally, as both rebate elements lead to the same consumers surplus for Sickness fund II, Firm A would only offer the rebate element that leads to higher profits. As described in equation (40) the profit of Firm A is $(1 - r_s\bar{p}_A)r_s\bar{p}_A + (1 - r_s p_s)r_s p_s$. It can be shown that for $t \geq \frac{1}{8}\left(5 + \sqrt{73}\right)$ the rebate element r_s^5 always generates higher profits. Therefore, we can define r_s^5 as the critical rebate element $\hat{\hat{r}}_s = r_s^5$.

IV.8 References

Badtke, F., (2007), "Die kartellrechtliche Bewertung des ‘AOK-Modells‘ beim Abschluss von Rabattverträgen." *Wirtschaft und Wettbewerb*, Vol. 7 and 8, 726-737.

Bauer, E., (2008), "Apotheken.", *In Schöffski, O., Fricke, F.-U., Guminski, W. (ed.), Pharmabetriebslehre, Springer-Verlag*, Berlin, Heidelberg, New York et al.

Brekke, K.; Königsbauer, I., Straume, O. R. (2007), "Reference Pricing of Pharmaceuticals.", *Journal of Health Economics*, Vol. 26, No. 3, 613-642.

Bundesministerium für Gesundheit, (2004-2009), "Vorläufige Rechnungsergebnisse der Gesetzlichen Krankenversicherung nach der Statistik KV 45", Bonn.

Cabrales, A., (2003), "Pharmaceutical Generics, Vertical Product Differentiation and Public Policy.", *UPF Working Paper*, No. 662.

Carradinha, H., (2009), "Tendering Short-Term Pricing Policies and the Impact on Patients, Governments and the Sustainability of the Generic Medicines Industry.", *Journal of Generic Medicines*, Vol. 6, No. 4, 351-361.

Court of Justice of the European Communities, (2009), "Case C-300/07: Judgment of the Court (Fourth Chamber) of 11 June 2009 (Reference for a Preliminary Ruling from the Oberlandesgericht Düsseldorf — Germany) — Hans & Christophorus Oymanns Gbr, Orthopädie Schuhtechnik v AOK Rheinland/Hamburg (Directive 2004/18/Ec — Public Supply Contracts and Public Service Contracts — Statutory Sickness Insurance Funds — Bodies Governed by Public Law — Contracting Authorities — Invitation to Tender — Manufacture and Supply of Orthopaedic Footwear Individually Tailored to Patients' Needs — Detailed Advice Provided to Patients)," Court of Justice of the European Communities.

Denda, R., (2010), "Steuerung im Arzneimittelbereich: Dreißig Instrumente in dreißig Jahren.", *Pharmazeutische Zeitung*, No. 10.

Grabowski, H., Mullins, C.D., (1997), "Pharmacy Benefit Management, Cost-Effectiveness Analysis and Drug Formulary Decisions.", *Social Science & Medicine*, Vol. 45, No. 4, 535-544.

Grilo, I., Shy O., Thisse, J.-F., (2001), "Price Competition When Consumer Behavior Is Characterized by Conformity or Vanity.", *Journal of Public Economics*, Vol. 80, No. 3, 385-408.

Hermann, C., (2007), "Sechs Monate Rabattverträge: Erste Ergebnisse aus Sicht der GKV," In EUROFORUM-Konferenz "Arzneimittelpreisbildung", Berlin: EUROFORUM Deutschland GmbH.

INSIGHT Health GmbH & Co. KG., (2009), "NationaleVerordnungsInformation (NVI)," Waldems-Esch.

KV Sachsen, (2011), "Richtgrößenprüfung Arzneimittel (RGP AM)". http://www.kvs-sachsen.de/mitglieder/kvs- mitteilugen/2011/032011/information-der-pruefungsstelle-der-aerzte-und-krankenkassen-sachsen/?drucken=1 [Accessed: October 27th 2011].

Merino-Castelló, A., (2003), "Impact of the Reference Price System on the Pharmaceutical Market: A Theoretical Approach", *Departament d'Economia i Empresa, Universitat Pompeu Fabra, Working Paper*.

Mestre-Ferrándiz, J., (2003), "Reference Prices: The Spanish Way.", *Investigaciones Económicas*, Vo. 27, No. 1, 125-149.

Miraldo, M., (2005), "Reference Pricing and Collusive Behaviour", University of York, York.

Natz, A., (2008), "Rebate Contracts: Risks and Chances in the German Generic Market.", *Journal of Generic Medicines*, Vol. 5, No. 2, 99-103.

Plate, F., (2009), "Rundschreiben zu Rabattverträgen vom 19.03.2009," *Bundesversicherungsamt*, Bonn.

Pro Generika e.V., (2010), "Vorschlag zur Neuordnung des Generikafähigen Arzneimittelmarkts der Gesetzlichen Krankenversicherung", *Pro Generika e.V.*, Berlin.

Pruszydlo, M.G., Quinzler, R., Kaltschmidt J., Haefeli, W.E., (2008), "Medizinische Probleme und Risiken bei der Rabattvertragsgerechten Umstellung von Medikationen in Deutschland.", *Deutsche Medizinische Wochenzeitschrift*, Vol. 133, No. 27, 1423-1428.

Schumacher, H.K., Greiner, W., (2008), "Festbeträge als Instrument der Ausgabensteuerung in der GKV - Systematik der Berechnung und resultierende Wirkungen.", *Gesundheits- und Sozialpolitik*, Vol. 62, No. 1, 53-64.

Schweitzer, S., (2006), „Pharmaceutical Economics and Policy“, *Oxford University Press*, New York, Oxford.

Spitzenverband Bund der Krankenkassen, Deutscher Apothekenverband, (2009), "Rahmenvertrag nach § 129 SGB V zwischen Krankenkassen und Apotheken," Berlin

Stargardt, T., Schreyögg J., Busse. R., (2005), "Arzneimittelfestbeträge: Gruppenbildung, Preisberechnung mittels Regressionsverfahren und Wirkungen.", *Das Gesundheitswesen*, Vol. 67, 468-477.

Zeiner, R., (2008a). "Vertragswettbewerb und Modellvorhaben als Strategische Optionen für Pharmaunternehmen - Teil 1.", *Pharm. Ind.*, Vol. 70, No. 5, 593-600.

Zeiner, R., (2008b), "Vertragswettbewerb und Modellvorhaben als Strategische Option Für Pharmaunternehmen - Teil 2.", *Pharm. Ind.*, Vol. 70, No. 6, 708-715.

Zeiner, R., (2008c). "Vertragswettbewerb und Modellvorhaben als Strategische Option für Pharmaunternehmen - Teil 3.", *Pharm. Ind.*, Vol. 70, No. 7, 817-824.

Zweifel, P., Crivelli, L., (1996). "Price Regulation of Drugs. Lessons from Germany.", *Journal of Regulatory Economics*, Vol. 10, 257-273.

V. The economics of research and development in the pharmaceutical industry

The ability to develop new products is essential for every entrepreneur in a market economy. Every form of market power is only temporary and local because as long as economical rents can be achieved in a market, there is still an incentive for competitors to enter. Nevertheless, research and development (R&D) play a special role in the pharmaceutical industry because R&D is not only driven by competitive forces in the market. Many companies in the industry define their entrepreneurial self-understanding over their ability to undergo R&D. Furthermore, the public expects that the pharmaceutical industry performs R&D and provides the market with a steady stream of new products that meet the medical needs. Therefore, the R&D activities of the pharmaceutical industry are under close observation.

The following chapter is organized as follows: Firstly, the market and its relevance shall be described. Secondly, the R&D process will be described in the context of the life-cycle of a pharmaceutical product. Thirdly, the social and political expectations towards the pharmaceutical industry are discussed. The chapter closes with a summary and an outlook about R&D in the pharmaceutical industry.

V.1 The economic position of the pharmaceutical industry

On economic-political grounds, the market for pharmaceuticals is an attractive subject and politicians seek to establish a prosperous industry in their countries. According to statistics of the German Association of the Pharmaceutical Industry (*Bundesverband der pharmazeutischen Industrie,* BPI), the worldwide sales for pharmaceuticals were US$ 961bn in 2012 and from 2000 to 2012 the nominal sales for pharmaceuticals increased by 8.5 % per year (see Figure 3). During this

time period, the world economy grew only by 6.8 % per year.[1] Such a development is not surprising because health is often seen as a superior good.[2] The World Health Organization (WHO) defines health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[3] This radical definition indicates that every person suffers under some kind of illness and it is just a question of budget, time, extent of inconvenience and relative risk if a treatment is conducted or not. In consequence, more consumption of health goods is possible when the standard of living increases and other essential needs are satisfied. Furthermore, with economic development comes in general a better social system which allows a higher consumption of health goods for a greater number of people. Hence, even though the data in Figure 3 shows a slowdown in growth from 2011 to 2012, which will continue in 2013 because of patent expiries for some top-selling drugs (so called "patent cliff"),[4] there is still high potential for the pharmaceutical industry especially in emerging markets. The largest developed markets (Western Europe, USA, Canada and Japan) still account for over two thirds of the world market and will continue to grow but their share is expected to decrease, because developing markets grow faster.[5] There is still a medical need in all parts of the world. Pharmacological options for many diseases are still underdeveloped. New findings in basic research (especially in genetics) enable new therapy options. Therefore, analysts see potential for an annual growth of 5.1 % for the pharmaceutical spending from 2013 to 2020.[6]

---

1 Based on data from IMF (2014)

2 See Hall & Jones (2007), p. 41

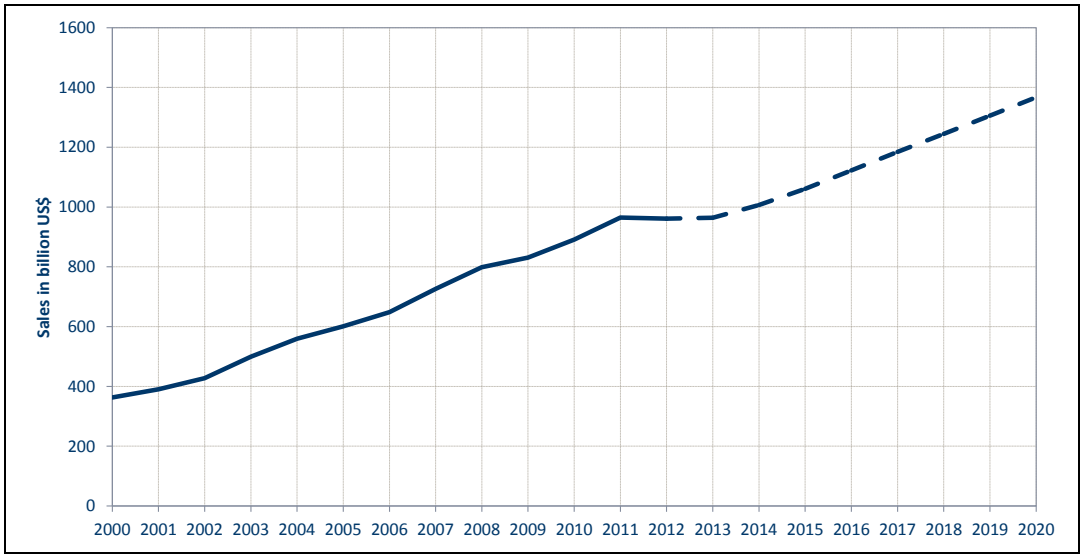
3 WHO (1948)

4 See Mullin (2013), p. 12

5 See vfa (2013), p. 13

6 See EvaluatePharma (2014), p. 7

Figure 3: Observed and projected development of sales in the world pharmaceutical market from 2000 to 2020



Source: BPI (2000 et sqq.), EvaluatePharma (2014)

The hopeful perspective for the future market development is one aspect that makes the pharmaceutical industry attractive. Its inner structure is another. The German Association of Research-Based Pharmaceutical Companies (*Verband der forschenden Arzneimittelhersteller*, vfa) presented in a national industry report some figures that underline this point.[7] The pharmaceutical industry is a leading-edge technology industry that needs qualified employees.[8] In 2012, academics accounted for 23 % of the workforce in the pharmaceutical industry, compared to 21.5 % in other leading-edge technology industries and 11 % in the manufacturing industry. Corresponding with the higher number of academics, the average incomes were 31 % higher than in the manufacturing industry. About 17 % of the workforce is employed in R&D compared to 10% in the high technology industry and 15% in the leading-edge technology (including pharma). The fact that women account for 50 % of the workforce in R&D, compared to 12 % in the engineering and 11 % in the automotive industry is in the light of gender equality an important social aspect.

---

7 The following data are from Institut der deutschen Wirtschaft (2013)

8 Definition leading-edge technology industry: R&D intensity (expenditures R&D per sales) is more than 8.5 %. High technology industry: R&D intensity 3.5 % to 8.5 %

Regarding its economic importance, the pharmaceutical industry is relatively small.[9] In 2012, its share of the German gross added value was 0.9 % (in comparison: automotive industry 4.0 % and engineering industry 3.6 %). This accounts for a production of 22.1bn euro. This value was generated by 120,000 employees, which is 0.3 % of all employees in Germany (in comparison: automotive industry 2.2 % and engineering industry 2.9 %). This means the employees were very productive. The gross added value per employee was 184,050 euro in 2012, as opposed to 119,000 euro in the automotive industry and 81,000 euro in the engineering industry. Such numbers make the pharmaceutical industry attractive for policymakers.

But the industry not only directly contributes to the economy, it also has played an important role in the improvement of health in the last decades. There are significant spillover effects by medical treatment as a healthier and longer living population is also more productive. Pharmaceuticals can also save cost for the health system because they can replace or avoid more expensive health care resources. There are various examples in the literature. Crémieux *et al.* (2007) estimated that an increase of $CAN 1.00 per capita in pharmaceutical spending can save $CAN 1.00 to 1.50 per capita for hospitals and other resources without decreasing life expectancy. Lichtenberg (2005) estimated that new drug launches accounted for 13 %- 40 % of increase in life-expectancy between 1986 and 2000. He calculated costs for gaining one life year (incremental cost effectiveness ratio, ICER) of US$2,250 to US$6,750. In comparison, the threshold of the English National Health Service (NHS) is £20,000 to £30,000 (US$30,000 to US$47,000) in regard of reimbursing a new drug.[10] Cutler and Kadiyala (2003) calculated that pharmaceutical treatment accounted for one third in reduced mortality results between 1950 and 1994 for cardiovascular diseases.[11] Jena and Philipson (2007) evaluated the economic gain through medical treatment of HIV/Aids. The life

---

[9] The following data are from Statistisches Bundesamt (2015)

[10] See Claxton *et al.* (2015), p. 5

[11] See Cutler & Kadiyala (2003), p. 156

expectancy for HIV/Aids patients increased about five years from the beginning of the epidemic in the 1980s to 2000. Given a value of life of US$ 100,000 and 1.5 million infected Americans, the authors calculated an aggregated social value of at least US$ 750 billion. Pharmaceutical producers captured only about US$ 70 billion of this value in form of profits and cost.

Governments appreciate industries that show high growth rates, create sophisticated jobs and contribute to the general well-being. A productive pharmaceutical industry and successful pharmaceutical research are both in the political interest. The pharmaceutical industry is supported through intellectual property rights, public funding and tax subsidies. However at the same time, the pharmaceutical industry is seen as a big cost factor (as shown for Germany in Chapter II) and some groups including regulators doubt if the delivered benefits are worth the cost. The pharmaceutical companies are accused of spending too much on marketing and too little on R&D. Their research programs were guided by profitability and not the medical need in society. Money is being spent for developing medicines to treat erectile dysfunction and hair loss but not severe infectious diseases in third world countries. Last but not least, the performance of animal tests and genetic experiments questions the ethics of pharmaceutical R&D.[12] In conclusion, pharmaceutical research must operate under the sight of strong support but also mistrust.

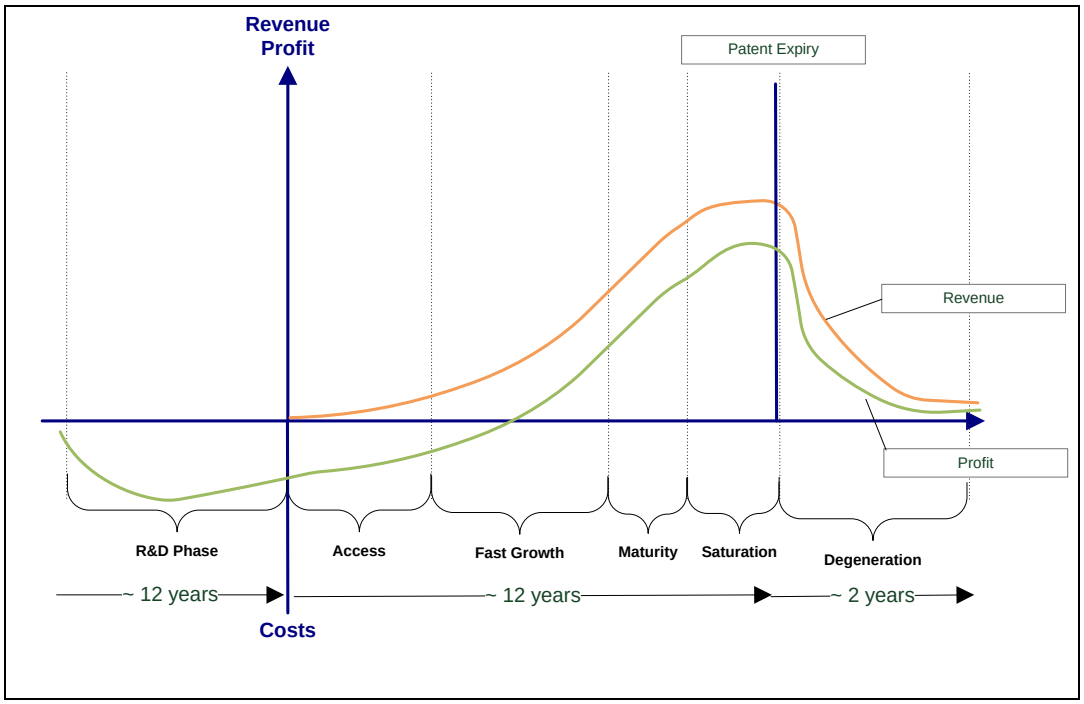
V.2 Pharmaco-economics during the life cycle of a pharmaceutical product

In the followings, the innovational process of a pharmaceutical product shall be described alongside its life cycle (see Figure 4). Roughly speaking, the life cycle of an innovative drug takes about 25 years. The ability to secure its intellectual property rights and to satisfy the requirements of the approval authorities are the crucial factors in the process. This will be discussed more deeply in this section.

---

[12] See Breyer *et al.* (2005), p. 452

Figure 4: Product life cycle for an innovative pharmaceutical drug



Source: Figure based on Raasch (2006), p. 15 and Guminski (2008), p. 201; R&D phase: Mestre-Ferrándiz *et al.* (2012), p. 39 and Kaitin and DiMasi (2011), p. 185; growth phase: Hemphill and Sampat (2012), p. 330; degeneration: Kanavos (2014), p. 234

V.2.1 R&D related types of pharmaceutical companies

It is important to point out that Figure 4 only describes the life cycle for a product of a research-based pharmaceutical company. It could be defined as the company that finances the whole R&D process (directly or indirectly) and brings the new molecular entity (NME) to the market. The following analysis will refer to this type of company. Though there are basically four more types in the market. Their differing product life cycles are presented here in short.

Parallel-import companies take advantage of price differences between the different national health systems within the European Economic Area (EEA: European Union plus Iceland, Lichtenstein and Norway).[13] They buy stocks of the originator (the research-based company) in market A, relabel the package, change

[13] Note: it is sometimes distinguished between parallel import, the import of a product produced abroad, and re-import, the import of a product originally produced in Germany. In the following, the mentioning of "parallel-import" also includes "re-import" as regulations are the same for both.

the patient information sheet and export it to a market B with a higher price level.[14] Hence, their product life cycles begin in the phase of fast growth when there is sufficient supply in other countries and normally they end with the patent expiry of the originator because, with the entrance of generic producers, the arbitrage between countries becomes too small.

Generic producers are normally responsible for the saturation and degeneration of the originator. They enter the market when the patent for a NME becomes public domain. They only have to go through an abbreviated market approval process. Larger generic producers might conduct limited R&D and develop new dosage forms or strengths. This also means that even though the product of the originator goes through a phase of degeneration a new phase of fast growth can begin for the generic companies.

Some companies are specialized on over-the-counter-drugs (OTC-drugs). These are pharmaceuticals that can be bought in pharmacies without a prescription from a physician. Hence, the market rules of normal consumer products can apply here. In the phase of degeneration, the originator might search for the switch from prescription status (short: Rx) to OTC, because in the OTC-market brand loyalty plays a bigger role and direct-to-consumer advertising is possible.[15]

A relatively new business model can be observed for companies of biotechnological drugs. Their life cycle is reduced to the R&D phase. They develop a NME up to the point where knowledge about efficacy and benefit become predictable. The NME is then sold to a larger established research-based company that has more experience and resources for the process of market approval and marketing.

Obviously, the boundaries between these different types of companies are fluid. The research-based company Bayer produces Aspirin® (active ingredient: acetylsalicylic acid), which may be the most well-known OTC product. The long-

---

[14] See Hancher (2004), p. 66

[15] See Raasch & Schöffski (2008), p. 224

established pharmaceutical company Roche (founded in 1896) has today a strong focus on biotechnology and Amgen (founded in 1980) as the largest specialized biotech company does not only develop new NMEs but goes through the whole life cycle process.[16] The second-largest generic producer Sandoz is owned by Novartis, one of the largest research-based companies in the world.[17] The Indian company Ranbaxy started as a contract manufacturer for active pharmaceutical ingredients (API). It began producing its own generics and recently launched its first original drug.[18]

In the following the different phases are discussed with a large research-based pharmaceutical company in mind. The first phase is the discovery of a new NME and the securing of its intellectual property.

V.2.2 Discovery phase and the economics of patents

In the beginning one needs basic research in understanding diseases and human physiology.[19] At this stage research is conducted mostly in public funded institutions, like universities and research centers, and discoveries are public knowledge. Based on this information pharmaceutical companies try "to identify a biological target whose pharmacological manipulation is expected to impact beneficially on a disease state".[20] When the pharmaceutical company receives a positive result it will optimize the new lead compound and first run safety tests regarding absorption in the blood, distribution in the body, effective metabolism,

16 See Kleemann (2013), p. 571

17 See Helfand (2013)

18 See Ranbaxy Laboratories (2012)

19 See PhRMA (2007), p. 2

20 Abou-Gharbia & Childers (2014), p. 5,526

excretion from the body and toxicity (ADME/Tox).[21] After this phase, the new active ingredient will be patented.[22]

Patents are granted property rights from a national or supranational agency that guarantees for limited time (20 years) exclusive use of an innovation within the jurisdiction of the agency. The product or process must have never been disclosed anywhere else and it has not been an obvious discovery.[23] Patents play an important role in many industries but they have a special (and sometimes controversial) status in the pharmaceutical industry. The reason is the direct link between patent and final product. For example, in the electronic industry cross-licensing and pooling is much more common because the actual competitive advantage lies in the manufacturing process and the ability to bring all these patents together in one marketable product.[24] The competitive advantage in the pharmaceutical industry is the ability to bring a potential product through the long and costly process of market approval. Because of that, vertical cooperation is more common. Small companies provide their innovative research and large pharmaceutical companies their ability to conduct large clinical studies and to go through the approval process. However, the manufacturing process for a pharmaceutical is quite simple and easy to replicate once the product is in the market. Hence, the intrinsic intellectual value of patents is more important and they are seen as the major instrument to ensure a sufficient incentive for innovation in the pharmaceutical sector. Only through the temporary monopoly the manufacturer can refinance the expenses of the R&D process.

Obviously, a market regulation like a patent leads to critical remarks since a monopoly causes a dead weight loss in the market, as the company will charge a price above marginal cost. Such extra profits attract rent seekers and forces companies to waste resources in defending their position. Parallel import

---

21 See PhRMA (2007), p. 4

22 See Lilly Pharma (2013)

23 See Lehmann (2003), p. 2

24 See ibid.p. 7

companies are one example for rent seekers, because the willingness to pay differs between countries and so do monopoly prices. With a patent, the innovator also always reveals a part of its knowledge and competitors can develop similar but still patentable alternatives (so called "me-too" drugs). In addition, the government can be a rent seeker when it installs price regimes to ensure politically acceptable price levels.[25]

But there are also methods of pharmaceutical companies that are widely questioned. Building a cluster of patents around the pharmaceutical product is a general concept. According to European Generic Medicines Associations (EGA), the average pharmaceutical product is protected by 20 to 40 patents. Besides the active ingredient itself, the manufacturer can also patent processes, formulations, the first use of the active ingredient in a therapy and other characteristics.[26] This way the manufacturer tries to create an evergreen thicket of patents that protects the product even after the core patent for the active ingredient expired.[27] The patenting of all aspects around the development of an active ingredient slows down the diffusion of knowledge and hampers the research process.[28]

Based on these negative welfare effects, alternatives for the patent system are discussed. Grootendorst (2009) presents alternative concepts, existing in form of pull (monetary rewards) or push (subsidies for research) programs. The patent itself is a pull program, because it rewards through a higher profit in comparison to a competitive market. One proposal for a weaker pull program is a limitation of four years for market exclusivity. Later generic entries have to pay royalties to the originator. Linking reimbursement to the benefit of a drug is another suggestion. The innovator receives a lump sum or price markup when a predefined standard is met (e.g. the social value), but the knowledge becomes public domain. Such an approach raises the question of how the social value of a new drug should be

25 See Grootendorst (2009), p. 314

26 See EGA (2007) and European Patent Office (2013)

27 See Jacob (2008), p. 7

28 See Raasch (2006), p. 31

defined. Kremer (1998) suggests an auction. But the highest bidder does not automatically receive the patent. After the auction a coin is tossed (not necessarily a fair coin). When the bidder loses, the government pays the highest price and the patent becomes public domain. Others favor the concept of value-based pricing as it is already in place in some countries. Pull programs can already be observed in daily practice, even though they do not replace the patent. The early benefit evaluation (discussed in chapter V) is one example of value-based pricing. The Advanced Market Commitment (AMC) program for the development of vaccines for diseases in third world countries is an example for rewarding research with premiums.[29] The AMC program guarantees a certain price level for the manufacturers. In return, they must agree to supply a certain annual quantity over ten years.

Push programs would subsidize the research process or fund clinical trials directly. This would also compensate underinvestment from private companies if they cannot fully consider and commercialize the spillover effects of their research.[30] It is also recommended that universities participate stronger in basic research. The results would be public domain. From a financial point of view such programs would move expenditures from the social health care system to the tax system. In countries with separated financial households for the two systems (like in Germany), this transfer of buget might not be easy to achieve.

V.2.3 The route to market approval

Right after the discovery of a potential drug, the manufacturer does not yet have proof that it will also work in the human body and that it is safe to use. It is in the economic interest of the manufacturer to conduct additional trials before bringing his product on to the market. But the legislator also has an interest in preventing harm to its people. Incidences like the elixir sulfanilamide tragedy (1937) in the US or the Contergan® scandal (1961) in Germany raised awareness for drug

[29] See UNICEF (2013)

[30] See Arrow (1962), p. 618

safety.[31] Agencies like the American Food and Drug Administration (FDA) in the US, the European Medicines Agency (EMA) or the German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) examine if a new drug fulfils the criteria for quality, safety and efficacy. Hence, the manufacturer has to make sure that his clinical trials are in line with the regulations of these agencies.

Even though the different agencies are independent, international standards of good practice for laboratories (GLP), good practice for clinical trials (GCP) and good practice for manufacturing (GMP) ensure similar requirements[32] and the major agencies (FDA and EMA) try to harmonize processes.[33] Nevertheless, it is possible that a new drug might receive market approval only in one region [34] or that the agencies differ in the specific approved indications.[35] First regulations on the European level were introduced in 1965. The current system of market approval in the European Union (EU) was established with the founding of the EMA in 1995.[36] Within the European Union (EU) there are four different paths for market approval: a central procedure (CP) by the EMA (also valid for Iceland, Lichtenstein and Norway); a national procedure by the local agency (BfArM in Germany); a mutual recognition procedure (MRP) or a decentralized procedure (DCP).[37] For MRP a product must already be authorized in at least one member state on a national basis.[38] Regulation (EC) No 726/2004 is the legal ground for the central procedure. The national and decentralized procedures are defined

---

31 See Schnee (1979), p. 23 and Cassel & Ulrich (2012), p. 51

32 See de la Haye & Gebauer (2008), p. 106-109

33 See Howie *et al.* (2013)

34 See Taylor (2010)

35 See Trotta *et al.* (2011), p. 2,266

36 Note: The EMA was originally founded as the European Agency for the Evaluation of Medicinal Products (EMEA)

37 See Schamp *et al.* (2008), p. 137-143

38 See BfArM (2013)

through Directive 2001/83/EC, which assembles the European regulations codified since 1965 in one single text. In daily practice, the central procedure is the standard path for drugs with a new molecule entity, especially because it is compulsory in all major fields of today's research (cancer, (auto-) immune dysfunctions, orphan drugs (drugs for rare diseases), biotechnology drugs, gene-therapy etc.) since 2004.[39] Therefore, the following remarks will refer to EMA and FDA only.

Pre-Clinical Phase and Clinical Phases I to III

Pre-clinical tests determine if a drug is safe enough for human testing.[40] Again vitro and vivo ADME/Tox tests are conducted to understand how the drug works and what its safety profile looks like. The company has to hand in the official application (FDA: Investigational New Drug application (IND); EMA: Marketing Authorization Application (MAA)) based on the results.

In the clinical phase I, the drug is tested with 20 to 100 healthy patients. The focus of interest is human safety, pharmacokinetic (absorption, metabolism and extraction) and pharmacodynamics (desired and side effects). When the drug shows no unacceptable toxicity, clinical phase II begins. The drug is tested by patients (from 100 to 500) with the disease or condition being studied. The manufacturer is interested to know if the drug shows the expected effectiveness. The researchers try to find the correct dose strength and intake schedule. Also short-term side effects are examined. Under specific circumstances (for example for very severe diseases), the agencies might already grant market approval (FDA: accelerated approval; EMA: approval under exceptional circumstances and conditional marketing authorization), meaning that the clinical trials continue but the manufacturer is allowed to bring his product on the market.[41] Phase III studies increase the investigated patient groups from several hundred up to 3,000 people

---

39 See EMA (2014)

40 The following paragraph is mainly based on PhRMA (2007)

41 See Hartmann *et al.* (2013), p. 119

and more. These numbers are necessary to generate statistically significant data about safety, efficacy and the overall benefit-risk relationship of the drug. Labeling instructions are also based on this phase.

Phase III is the most expensive and most time consuming clinical phase (only the preclinical phase takes longer). The members of the Pharmaceutical Research and Manufacturers of America (PhRMA) spent about one third of their research costs in phase III in 2012 (Table 18). Therefore, it is not surprising that the success rate is lowest in phase II. When doubts arise about the efficacy and commercialization potential, the project is terminated.[42] This also saves money for Phase IV trials. They are conducted after market approval to investigate long term effects and possible line extensions (see page 146 for details).

Table 18: R&D by Function, PhRMA Member Companies - 2012

Function	**Total Expenditures in million US$ (2012)**	**Share in %**	**Average time in years**	**Success rates to enter the next phase in %**
Prehuman/Preclinical	11,816.3	23.8	3.9	35
Phase I	3,823.3	7.7	2.1	54
Phase II	5,756.2	11.6	2.2	34
Phase III	15,926.8	32.1	2.4	70
Approval	3,834.6	7.7	1.2	91
Phase IV	6,776.5	13.7		
Uncategorized	1,653.8	3.3		
Total R&D	49,587.6	100		

Source: total expenditures: PhRMA (2014), p. 71; average time: Mestre-Ferrándiz *et al.* (2012), p. 39, Kaitin and DiMasi (2011), p. 185; success rates: Paul *et al.* (2010), p. 206

[42] See Abou-Gharbia & Childers (2014), p. 5,541

Approval Process

After the completion of all clinical phases, the manufacturer asks for market approval (FDA: New Drug Application (NDA) for small molecules or Biologics Licence Application (BLA) for biotechnological drugs; EMA: still MAA). The agency has to decide if the contributed data proves effectiveness and that there is an acceptable balance between risk and benefit. However, the agency must also decide what intake information is necessary for the physicians and it must assess whether the manufacturing process preserves the drug's identity, strength and purity.[43] With approval, the agency also defines the therapeutic indication and other prerequisites for the usage. This is an important aspect regarding liability and marketing. In general, the manufacturer is only responsible for damages within the approved indication but so is his right for promotional activities. A physician acts on his own behalf using the drug in another indication (so called "off-label-use").

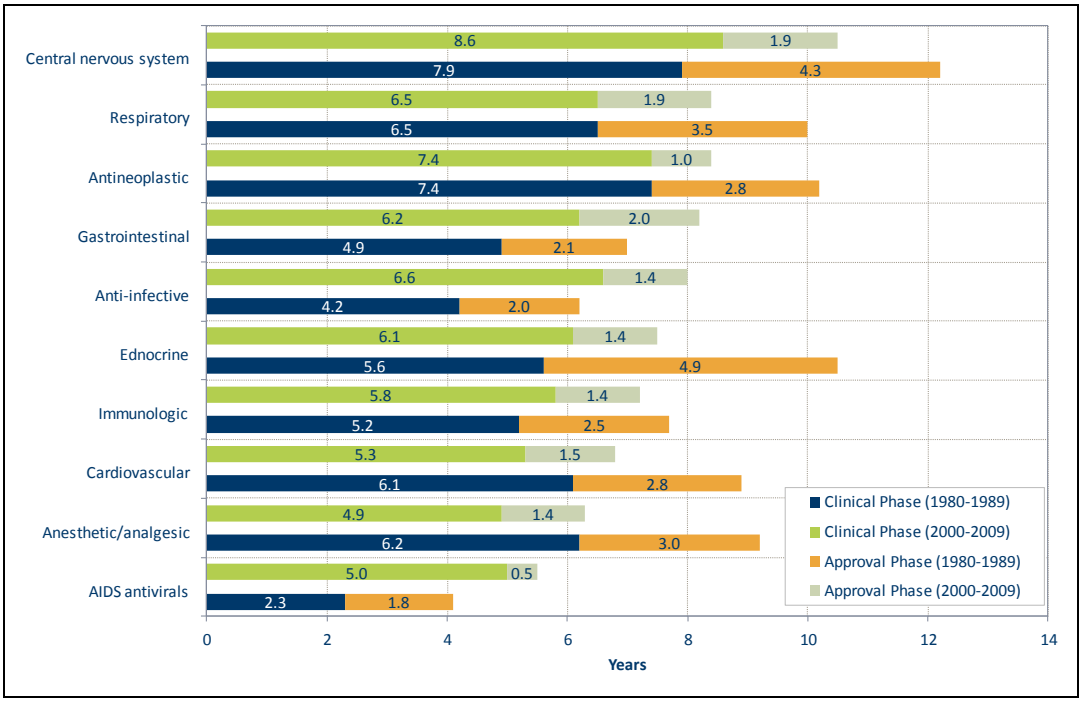
The process of market approval has a severe influence on the investment decision and the innovation ability of pharmaceutical firms. Over 11 years can pass from the patenting of an active ingredient (see Table 18) until the manufacturer is allowed to market his product. Furthermore, a drug that achieves market approval also has to refinance the costs of failed projects. A current study by Mestre-Ferrándiz *et al.* (2012) estimated costs of about US$ (2011) 1.5 billion for the development and approval of one drug. But only a share of 16 % of these costs accounted for the actual research for this particular drug. The majority incurred for failed projects (44 %) and large opportunity cost (40 %) because of the long research and approval phase, that needs to be pre-financed.

The system of market approval is an obvious market entry barrier and pharmaceutical companies have a high interest in a short process and predictable outcomes. In regard of the administrative process, the approval time was significantly reduced (see Figure 5) in the last decade. Legislative changes like the Prescription Drug User Fee Act (PDUFA) from 1992 in the US supported this

[43] See PhRMA (2007), p. 8

development.[44] The global standardization regarding research and clinical trials also creates a kind of competition between the agencies. When a drug has been approved in one major market, the other agencies can face public pressure to speed up their processes.[45] Regarding the clinical phase, the development is not that clear. For most therapeutic classes listed in Figure 5, the clinical phase increased. There is a tendency for higher demands regarding the size of clinical trials and the information that need to be extracted and presented.[46]

Figure 5: Mean clinical and approval phase times for new molecular entities and significant biologics by therapeutic class in the USA, decade 1980-1989 and 2000-2009



Source: Own presentation based on Kaitin and DiMasi (2011), p. 186-187

In order to compensate for the long approval process, there are additional regulations ensuring market exclusivity for a specific time. In the EU, pharmaceutical companies receive a supplementary protection certificate (SPC)

44 The FDA was now allowed to collect fees from the manufacturers for the approval process; in return the FDA had to meet certain performance benchmarks.

45 See for example Howard & Feyman (2014)

46 See Beishon (2014), p. 14

for additional five years (with a maximum of 15 years between market approval and the end of the SPC).[47] Since 2006, the manufacturer can receive an additional six months if he applies for pediatric extension of his drug.[48] At the same time, the manufacturer receives a data exclusivity of eight years for documents handed in for market approval and additional two years (or three years if a new indication was registered in the first eight years since first market approval) of market exclusivity.[49] Orphan drugs receive an even stronger form of market exclusivity. In the first ten years after market approval no other pharmaceutical company can obtain market approval for the same orphan disease as long it does not provide significant improvement in therapy.[50] The US has similar regulations to ensure a specific period of market exclusivity.[51]

As the patent system, the concept of market approval also raises criticism. The idea behind the system is to protect citizens from ineffective drugs. However, some argue that the possible damage is minimal compared to the losses in health the system can cause. The delay until an effective drug receives market approval is one loss. In the meantime people might die who would have benefited from that drug. Other promising drugs might never reach the market because the number of patients is too small to compensate for approval related R&D expenditures. Clinical studies do not consider individual benefits. On average, a drug might be ineffective but it might have a positive effect for a small number of patients.[52] Backhaus (1983) for example proclaims that an effective liability system would be more helpful to prevent the market entry of ineffective drugs without causing a delay for effective ones. A regulatory agency might even be impedimental under such a system because it might be reluctant to admit a mistake in case of damage.

---

47 See Raasch (2006), p. 38

48 See Putzeist *et al.* (2013), p. 28

49 See EGA (2007)

50 See Westermark (2007), p. 332

51 See Schacht & Thomas (2002) and FDA (2009) for details.

52 See Henderson (2010), p. 47

On the other hand, the strong information asymmetry in the market is one important argument against the abolishment of agencies like FDA and EMA. Furthermore, often only under regulative pressure, do pharmaceutical companies conduct the necessary studies so that professionals can make a well informed decision.[53]

V.2.4 Market access and drug launch

Market approval does not imply direct market access. In nearly all national health systems (the US and Germany are prominent exceptions) a new drug is not directly available in the outpatient market because a responsible agency decides or negotiates about reimbursement and price level.[54] Delays through market authorizations and reimbursement regimes can also have a negative impact on the benefit of a drug.[55] Nevertheless, even in countries without direct price control, other instrument can slow down market penetration of new drugs.[56] Section II.1 elaborates on instruments in the German statutory health insurance system.

As already mentioned, the innovational process does not end with market approval. When the product is on the market, manufacturers continue to conduct studies. They have various intentions:[57] clinical trials (Phase IV studies) monitor long-term effects regarding safety, efficacy and side-effects; the manufacturer can seek approval of additional indications; the agency can demand them as a condition for the approval; national health system might request specific comparison studies in the context of reimbursement decisions. The manufacturer is also obliged to monitor and analyze reports about adverse effects.[58] Finally, the

---

53 See Ross (2007), p. 3,598

54 See Vogler *et al.* (2011), p. 52

55 See ECORYS (2009), p. 16

56 See Häussler *et al.* (2009), p. 334

57 See de la Haye & Gebauer (2008), p. 114

58 See Godet & Ferrand-Nagel (2002), p. 112

manufacturer conducts also non-interventional observational studies to generate epidemiological data about his drug in daily practice.

Observational studies are also an important marketing tool, because physicians are normally receiving some kind of compensation for participation. This gives an incentive to prescribe the new drug. Non-surprisingly, this led to criticism. In Germany, the regulations regarding observational studies were tightened in the last years. Pharmaceutical companies have to announce the execution (the related document must also hold information about the financial compensation for the participating physicians) and send a report to the BfArM at the end of the study.[59]

V.2.5 Patent expiry and generic entry

With the end of patent rights and data exclusivity, the product of the originator goes directly into the phase of degeneration. Within two years generic producers gain significant market share (in Germany about 85 %).[60] There are strategies to soften the fall in sales[61], but in the end, the development of a new patentable drug is the only profitable option. A new life cycle begins.

V.3 The hypothesis of declining R&D efficiency

There is a high public interest in the pharmaceutical industry providing a steady stream of new innovative drugs, and no other important industry spends so much for R&D relative to sales. Figure 6 shows the R&D intensity (R&D spending per sales) for the ten sectors that spent the most on R&D in 2012. Pharma/Biotech companies had an average intensity of 14.3 %, the software industry followed

---

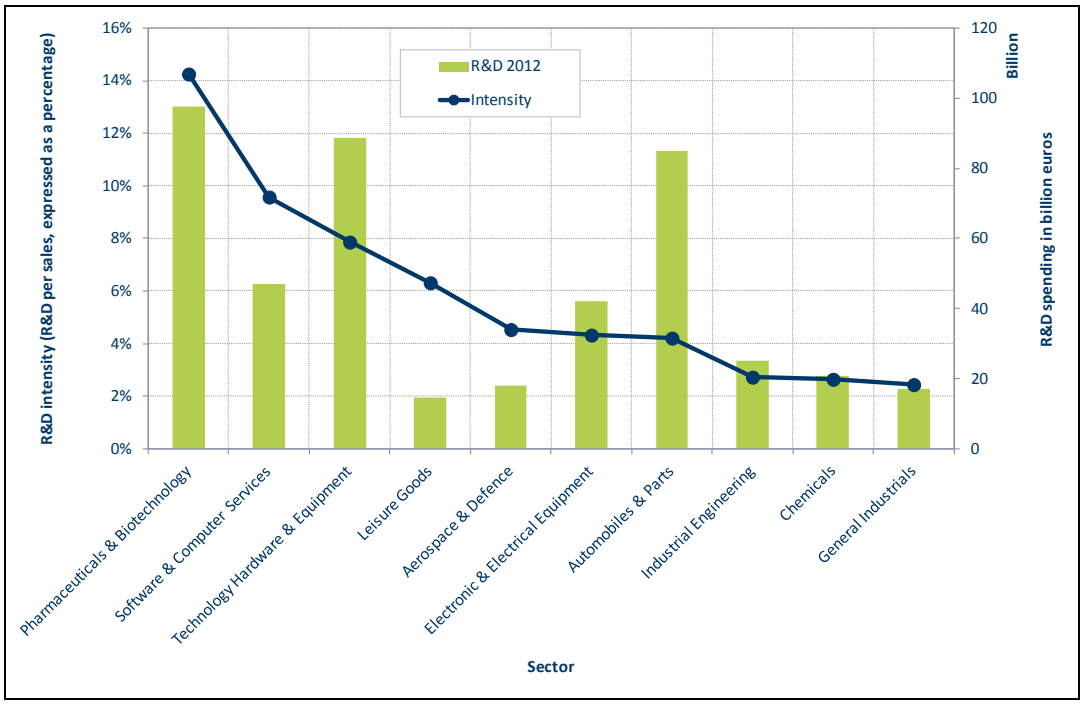
59 See GKV-Spitzenverband (2013)

60 See Kanavos (2014), p. 234

61 See Raasch & Schöffski (2008), p. 215-231 for an overview

with 9.6 %. Interestingly, from 86 companies in the EU scoreboard with R&D spending larger than sales, 69 were Pharma/Biotech companies.[62]

Figure 6: R&D spending and intensity (R&D per sales) in ten sectors, 2012



Source: Own calculation based on Hernández *et al.* (2013), p. 85. Sample of 2,451 firms out of the world Top2000 and EU Top1000 companies in R&D spending (companies without sales excluded)

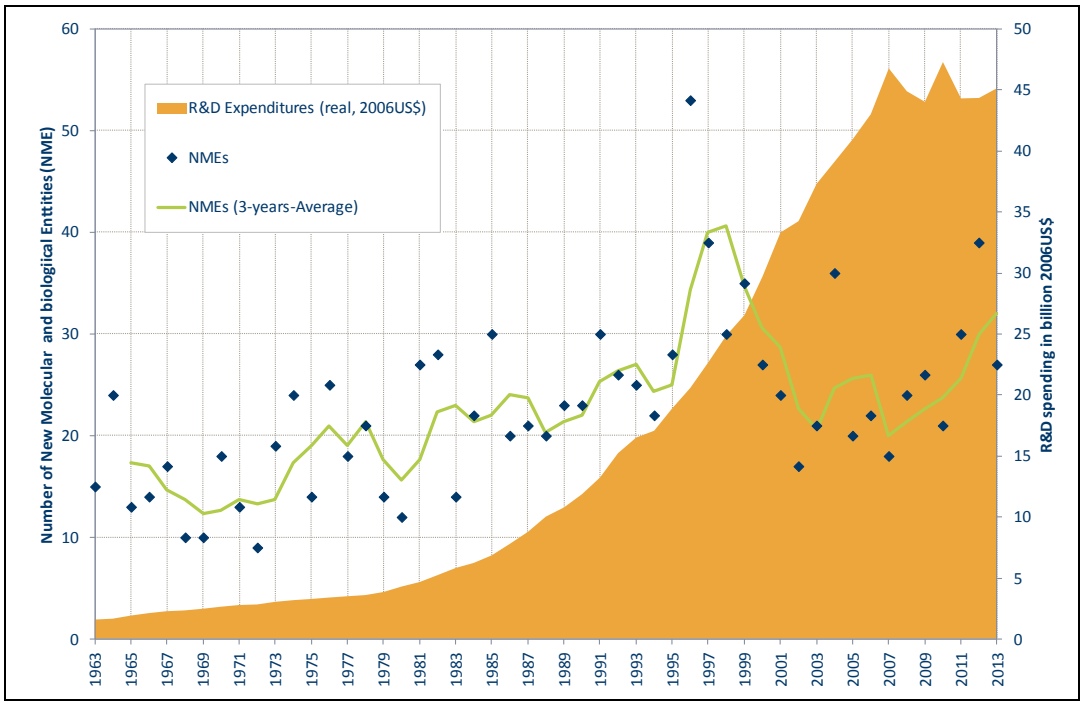
But even though the pharmaceutical industry spends a significant amount for R&D, there have always been market observers who doubt the innovation ability (and willingness) of the pharmaceutical industry.[63] Kesselheim *et al.* (2013) reviewed 42 studies analyzing the development in innovation (the studies cover a period from 1956 to 2010). Only 21 % studies concluded a positive trend in innovative drug development but 45 % a negative one. The remainder reached no conclusion. It indicates that the pharmaceutical industry has contributed to improvements in health but it could have done better. An often cited indicator for

62 22 companies with no sales information were excluded. Again a high number (eleven) were pharmaceutical companies.

63 see for example Virts & Weston (1980) or Sozialpolitischer Arbeitskreis Berlin (Sab) (1971a, 1971b)

the decreasing productivity is the money spent to develop one new drug. Data from the members of PhRMA about R&D spending and the reported market approvals for new molecules and biologicals by the FDA show a sharp increase in spending (in real terms) but a moderate development in the number of approved drugs (see Figure 7).

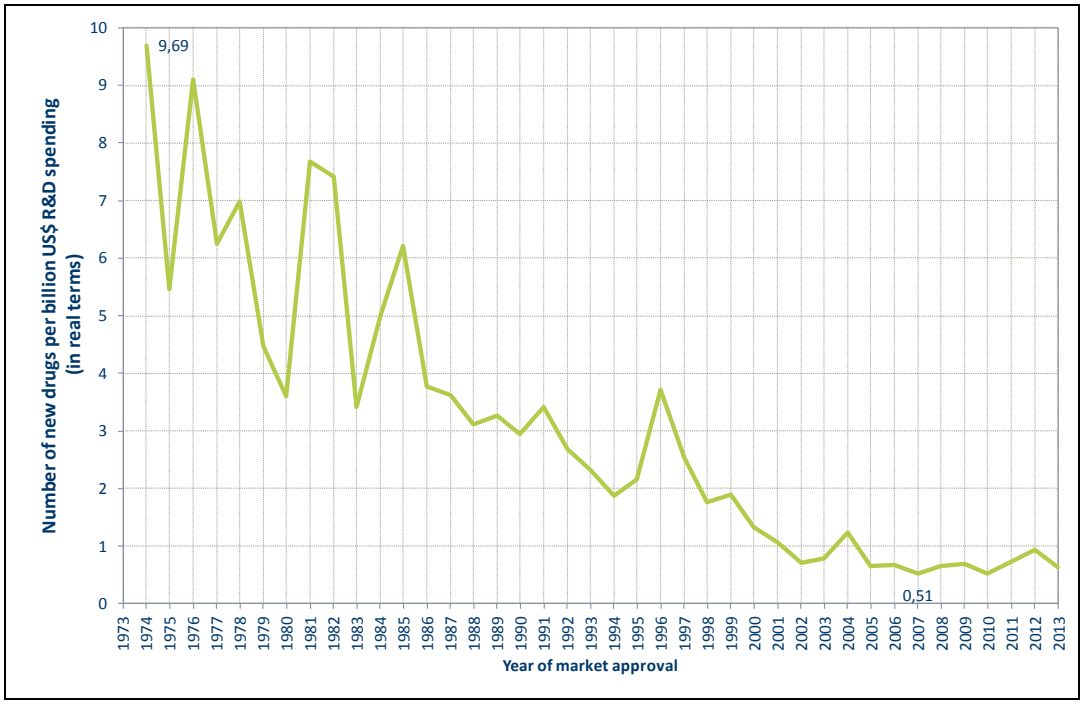
Figure 7: Development of R&D spending (PhRMA) and market approvals (FDA), 1963-2013



Source: Own calculation based on DiMasi (2008), FDA (2014), FRED (2014), PhRMA (2014)

Together with information from Table 18 (see page 142), this data can be used for a rough estimate of patent efficiency (drugs per billion US$). The average R&D expenditures are calculated based on the expenditures eleven (pre-clinical), seven (phase I), five (phase II), three (phase III) and one (approval) years before market approval and current year (phase IV and uncategorized) weighted by shares in Table 18. The results in Figure 8 show a declining trend for almost four decades. The low point was reached in 2007, since then the R&D efficiency remained relatively stable.

Figure 8: Overall trend in R&D efficiency (inflation-adjusted) considering delay between begin of research and approval



Source: Own calculation based on DiMasi (2008), FDA (2014), FRED (2014), PhRMA (2014)

Scannell *et al.* (2012) provided a sophisticated summary about the contemporary problems in pharmaceutical R&D. They also analyzed the development of the R&D efficiency using nearly the same data. They call their findings "Eroom's Law" in reference to the famous Moore's Law. While the latter postulates that the number of transistors in a dense integrated circuit doubles approximately every two years, Eroom's Law states that R&D efficiency has halved every 9 years since 1950. The authors identify four major and one minor reason for the observed declining in R&D efficiency. They call the problems (1) "better than the Beatles", (2) "cautious regulator", (3) "'throw money at it' tendency" and (4) "'basic research – brute force' bias". (5) "Low hanging fruits" are seen as a minor problem. The first problem (1) expresses that every new drug reduces the economic value for all undiscovered active ingredients, because regulators and physicians only accept new products that show some additional value. The fifth problem (5) says that every new drug is more difficult to develop than the last one. The authors value (1) more than (5) because even with today's methods,

there are still a lot of undiscovered therapy options. Pharmaceutical companies react to the first problem by moving R&D to diseases that are more difficult to address pharmacologically. The more complex a treatment becomes and the more established therapy options exist, the more regulators are cautions (2). Every scandal tightens regulation and there is a general mistrust regarding the honesty of the pharmaceutical industry when it presents the value of its products.

Because of the high first-mover advantage, there is an incentive to increase R&D budgets even when it turns out to be inefficient afterwards (3). R&D is also a stochastic and long process. This makes it difficult to identify where in the process money is best spent and high profits allowed globally increasing budgets without the urge to identify inefficiencies.

Since the early 1990s, high-throughput screening (HTS) is established in the pharmaceutical industry (4). It allows automatic screening of 100,000 and more molecules in a short time. Scannell and his co-authors doubt that the method has led to a productivity gain as success rates for clinical trials remained quite stable over time. They prefer the older iterative approach that might be slower but requires less steps to succeed.[64] The authors state that there are approaches to combine the two methods. In summary, the trend in Figure 8 is negative because (marginal) R&D cost increases but at the same time probabilities for market approval do not.

The described problems of Eroom's Law lead to several symptoms that increase costs further. Firstly, study designs focus on very specific hypotheses, ignoring other positive results. Secondly, the additional benefits of new drugs decrease and clinical trials therefore need larger number of participants to deliver the same statistical power as older drugs. Thirdly, the clinical trials become narrower focusing on precise effects, but the regulators demand more of them and they take longer.

---

[64] They compare it with guessing one word out of the English language. It is more effective to ask 20 subsequent questions (with only "yes" and "no" as answers) than to write down 20,000 words out of 600,000 and ask if the one searched for is among them.

The opinion paper of Scannell et al. (2012) is based on data from 2010. They expected no further decrease in productivity for the next five to seven years because R&D focuses more on cancer, orphans and biologicals where the described problems are less severe. The data in Figure 8 supports their prediction.

The work of Scannell *et al.* (2012) summarizes the resource and transaction cost-based arguments for the declining productivity in R&D. The "'throw money at it' tendency" also indicates that the pharmaceutical industry has a high free cash flow that is not used efficienly. Jensen (1986) argues that in such a case the free cash flow should be extracted to the capital market and channeled into more promising projects, instead of investing it into low-return projects within the company. In fact, pharmaceutical companies are in a process of vertical disintegration. The basic research process is outsourced to smaller companies and strategic alliances are formed, especially with the biotechnological industry. This way, the financing is externalized to the capital market. In the opinion of Gleadle *et al.* (2014) this leads to a "financialisation" of the pharmaceutical industry and explains the decreasing efficiency. Financialisation is defined here as a "change in strategic priority from delivering value to customers (in the form of marketable products) to delivering value to creditors and shareholders (in the form of distributable profit or financial instruments saleable at profit)".[65] Investing pension funds are more risk averse and their investment horizon is shorter (3-5 years) than the R&D process (10 to 15 years), so a business strategy oriented to the financial market can have a negative effect on the decisions about research projects. Gleadle *et al.* (2014) are uncertain if the current development is a transition phase or persistent. In the 1990s, pharmaceutical companies adopted the "blockbuster strategy". R&D focused on products that promised worldwide sales of at least US$ one billion. This strategy seems to have come to an end and pharmaceutical companies have to restructure.[66] Critics of the pharmaceutical industry would say that the financialisation of the pharmaceutical industry is a much older phenomenon.

---

[65] Gleadle *et al.* (2014), p. 71

[66] See Montalban & Sakinç (2013), p. 1,023

Nearly all large pharmaceutical firms are public companies and they have shown above average profit returns for a long time. This suggests rather an oligopolistic than a competitive market despite the relative low market concentration. In that regard, a strong regulation could be in the interest of the industry because strong patents and market authorization might increase market entry cost but at the same time support local monopolies.[67] The average operating profit margin for pharmaceutical companies that are members of the S&P 500 stock index has remained above 18 % since 1995. At the end of 2013, the pharmaceutical companies had reached 22.7 % compared to 8.8 % for the complete health care sector and 6.7 % for consumer staples. The information technology industry reaches similar margins (16.8 % end of 2013), but they are far more volatile.[68] Despite all structural problems, the pharmaceutical industry was able to remain a very profitable business over a long time. Resource based as well as finance based arguments deliver valid explanations for the current state of the pharmaceutical industry.

V.4 Controversies about efficient use of funds by the pharmaceutical industry

Empirical analyses often identify a negative impact of regulatory instruments on the overall output of new drugs.[69] These results are not surprising because lower profits leave less money to invest into R&D. However from a more general point of view, this might be a reduction in quantity but not necessarily in quality. After all, pharmaceuticals are only one of many inputs in the provision of care and every euro handed over to the pharmaceutical industry cannot be spent somewhere else. Therefore, discussions about the innovation ability of the pharmaceutical industry are also discussions about the allocation of health

---

67 See Spitz & Wickham (2012), p. 6

68 See Yardeni & Abbott (2014), p. 7-11

69 See for example Giaccotto *et al.* (2005) and Lichtenberg (2007)

services in general. Especially since health care can have significant spillover and multiplier effects on the entire economy.[70]

A pure market solution cannot solve the allocation problem because various forms of market failure exist in the health market.[71] For example, vaccines have an external effect on the health of others and become a form of public good. There is also a significant information asymmetry. The patient must trust the opinion of the physician, as it is difficult for a patient to gain better information through experience. Many treatments for chronic diseases cannot cure but only reduce the probability of a negative event. The patient cannot observe causality between taking a pill and the prevention of a heart stroke. Therefore, patients and payers want to have the certainty that the therapeutic choice of a physician is based on objective criteria.

Because of these circumstances, decisions of pharmaceutical companies about R&D investments and marketing activities are under special observation by the public. Pharmaceutical companies often face the accusation of spending more on marketing than they do on R&D, even though the USA and New Zealand are the only industrial countries that allow direct to consumer (DTC) marketing for prescription drugs.[72] In 2010, the pharmaceutical industry spent approximately US$ 27.7 billion for promotion in the USA alone (see Figure 9). Free samples for physicians accounted for half of the promotion costs. The direct contacts with physicians (detailing) accounted for 21.1 % of all promotion costs[73], whereas hospital detailing accounted only for 1.7 %. Advertising in professional journals represented a share of 1.2 % while conferences and meetings accounted for 10.3 % of the promotion costs.

---

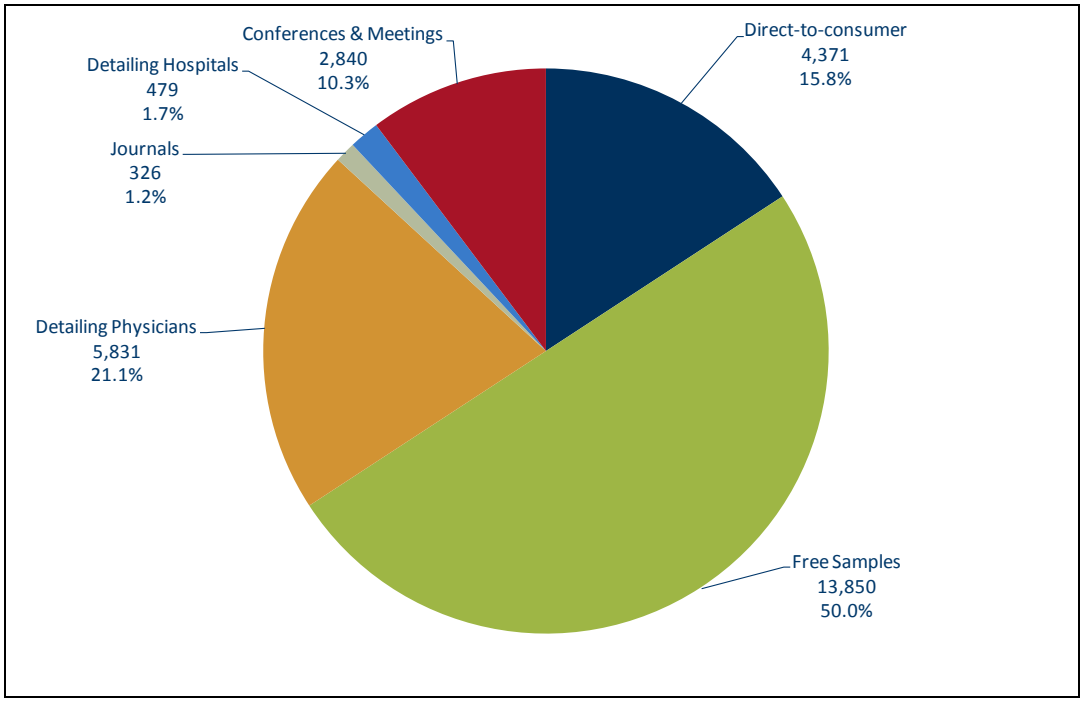
70 See Breyer *et al.* (2005), p. 6

71 See chapter 5 in Breyer *et al.* (2005) for a detailed look

72 See Spitz & Wickham (2012), p. 10

73 Including so called “ePromotion”

Figure 9: Pharmaceutical promotion to consumers and providers in the US (million US$), 2010



Source: Own calculations based on Kornfield *et al.* (2013), p. 71

Observational studies (phase IV) are not counted as promotion. They are part of the R&D budget, which was US$ 40.6 billion for the PhRMA members in the United States in 2010.[74] These numbers indicate that pharmaceutical companies spent significantly more on R&D than marketing. However, there are also estimations that about 30 % of promotion costs are unmonitored and that official R&D costs are overestimated because studies serve marketing purposes.[75] Data analysis based on fiscal reports does not give a clear answer because marketing activities are summarized under "selling, general and administrative" (SG&A). In general, expenditures for SG&A are higher than for R&D in the pharmaceutical industry.[76] The share of SG&A on sales is also relatively high compared to other

[74] See PhRMA (2012), p. 54. Total spending was US$50.7 billion in 2010 for PhRMA members. Compare also to Figure 7. The graph shows the value for 2010 in real terms: 2006 US$ 47.26 billion

[75] See Gagnon & Lexchin (2008), p. 29

[76] See for example Mahan (2002), p. 3 and Weiss *et al.* (2009), p. 534

industries, but the ratio between SG&A and R&D is lower.[77] Nevertheless, pharmaceutical companies spend a significant amount on advertising and that is why complaints of the pharmaceutical industry often ring hallow when reforms affect profits.

Critics argue that as long as the pharmaceutical industry still has money left for advertising, there is no reason why new regulations should lead to less R&D expenditures. In general, R&D and advertising are strongly linked.[78] The benefit of a new safety system in a car will not (or only slowly) diffuse in the market, without a campaign that emphasizes heavily on the new feature. Theoretically, the same applies to pharmaceuticals. A novel drug will not penetrate the market as long as the physicians do not know about it. But in opposite to a car novelty, a lot of public (and objective) information exists. Nearly all results of clinical studies for market approval require publishing in academic journals. Regulators publish their opinion on the effectiveness of a new drug with their reimbursement decisions. Medical societies issue clinical guidelines and revise them regularly. Physicians are committed to continuing medical education (CME). In the light of this information, regular visits from sales representatives handing over free samples are regarded as dispensable. Physicians often claim that they are immune to persuading advertising but studies show otherwise.[79] Hence, the promotion of pharmaceuticals through advertising is seen as a market distortion.

But even when pharmaceutical companies do not "waste" their budget on marketing, the question remains if investments in R&D are spent the right way. In Germany, the annual report of the pharmacologists Fricke and Klaus is a widely recognized source to answer the question about the level of innovation of a first-time launched drug. The authors categorize new drugs into four groups:[80] (A)

---

77 See Lowe (2013)

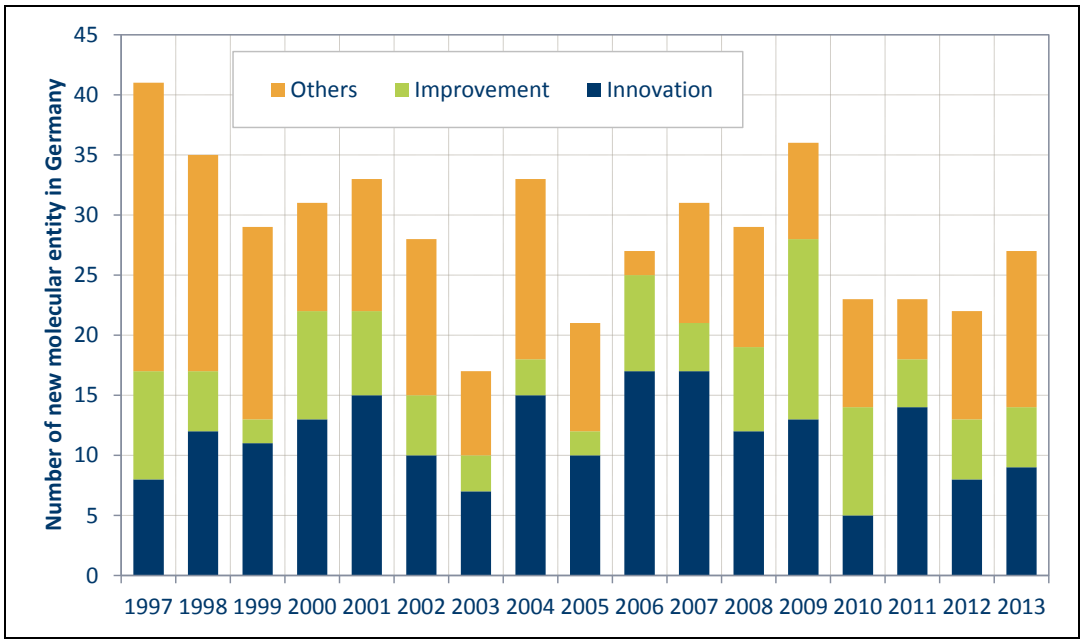
78 See Azoulay (2002), p. 586

79 See for example Azoulay (2002), Nair *et al.* (2010) and Venkataraman & Stremersch (2007)

80 See Fricke (2013), p. 3

Innovative structure or new mode of action with therapeutic relevance; (B) improvement of pharmacokinetic or pharmacodynamics properties of known modes of action; (C) analog drug with only small or marginal differences to already launched products; (D) no substantiated knowledge about mode of action or therapeutic value unclear. Combinations like A/C are also possible. Figure 10 presents the evaluation of NME launched since 1997 in Germany. During this period, 486 new active ingredients were analyzed and 40.3 % of them had a new mode of action.

Figure 10: Number of NME launched in Germany, grouped by classification of Fricke & Klaus, 1997 to 2013



Source: Fricke and Schwabe (2013), Fricke (2014); Innovation: A, A/C; Improvement: B; Others: C or D

The evaluation is mainly based on pharmacological criteria. Hence, a drug might be classified as innovative, but its medical benefit is not significantly better than that of alternative therapies on the market.[81] The classification system is also an example for the "better than the Beatles" and first-mover problem presented in

[81] See Kaber & Twarock (2009), p. 149

Section V.3. New discoveries of potential targets often lead to parallel research.[82] The company bringing the first product to market will receive an A, while every follower will only be granted a C. Even when the "C product" is most likely the result of parallel research, it still raises suspicion on being just a me-too and the consequence of a risk-averse R&D strategy. In other industries, step innovations and little variations between products are seen as a broader scope for consumer choices. They are considered misallocations in the pharmaceutical market.

Excluding the option of nationalizing the pharmaceutical industry, regulators can only give different incentives regarding the R&D output. A direct incentive is the public funding of research. The focus here is on basic research. New discoveries in pathogenesis and human physiology give pharmaceutical companies new approaches for their screening processes. Some criticize this division of work as socializing costs and privatizing profits.[83] The research and its discoveries is paid by tax money, the pharmaceutical companies can use the information for free and create profitable products based on this information. As it was shown in Table 18, a high percentage of potential drugs do not reach market approval. Public research can be a way to reduce the expenses for failed research projects by the pharmaceutical industry. However, public research could also be seen as investment by the state that will create revenues beyond the profits of the drug sales (see discussed example in Section V.1). Instead of undertaking research itself, health care systems can reward desired R&D results with faster market launch, benefit and cost related prices and generous reimbursement. But they can also punish undesired outcomes through reimbursement prices on level of generic alternatives, limit reimbursement to only specific indications and reward health providers by using cheaper and more established alternatives.

---

[82] See Häussler *et al.* (2002), p. 61

[83] See Light & Lexchin (2012), p. 2

V.5 Conclusion and outlook

It is difficult to get a clear picture of the situation of the pharmaceutical industry. On the one hand, the pharmaceutical market faces an increasing demand and is still highly profitable. New discoveries in genetic science open up possibilities for new pharmaceuticals in various indications. On the other hand, research-based pharmaceutical companies face structural problems that are to a certain extent "homemade" but also a consequence of society's expectations.

Regulative cornerstones for the business model of the pharmaceutical industry are intellectual property rights in form of patents, marketing authorization and most recently pharmaco-economic evaluations. There are wide-ranging opinions about the future arrangement of these regulative instruments. Some see them as necessary requirements to ensure innovation. Without patents, research-based companies cannot protect their innovations and lose the incentive for research. Marketing authorization prevents the development from ineffective drugs and guarantees safety. Pharmaco-economic evaluations route research programs through benefit related pricing and increase the transparency in the market. Others see these regulations as an impediment for innovations in the market. Patents diminish competition and reduce incentives to optimize processes. Marketing authorization reduces and delays the access to therapeutic options. Pharmaco-economic evaluations are abused as price cutters and work as a market entry barrier because they are conducted when full information about the benefit of a drug is missing.

The patent system seems not to be under supervision. In fact, it is sought to enforce stronger patent rights in emerging markets. Agencies for marketing authorizations increase the requirements but also use more options of conditional approval (recall Section V.2.3).[84] The marketing authorizations show a tendency to not only consider efficacy but the benefit of a drug. Nevertheless, pharmaco-economic evaluations remain in the responsibility of the national health systems

[84] See Putzeist *et al.* (2013), p. 25

because the evaluations are linked to national pricing and reimbursement schemes.

The research-based pharmaceutical industry reacts to these structural problems by putting a stronger focus on its ability to bring products to the market.[85] Basic research and first clinical trials (up to phase II) are outsourced to smaller firms and academic institutes. This way, a diversification of risks and a reduction in R&D personnel are possible. Mergers & Acquisitions are also an option but the pharmaceutical industry remains quite diversified. Some research-based companies also try to expand in the field of non-patent drugs.[86] Either they acquire generic producers or they plan the development of biosimilars.[87] The rising importance of pharmaco-economic evaluations and the transfer of R&D to smaller entities also change the content of the research pipeline. The focus is more on niches and rare diseases than blockbusters.[88] This could also increase again the productivity of research process. The future will show if these changes will improve the provision of health in the long run or if they only serve the capital market in the short run.[89]

V.6 References

Abou-Gharbia M & Childers WE (2014): Discovery of innovative therapeutics: today's realities and tomorrow's vision. 2. pharma's challenges and their commitment to innovation. *Journal of Medicinal Chemistry* 57(13), 5525-5553. DOI: 10.1021/jm401564r.

Arrow KJ (1962): Economic welfare and the allocation of resources for invention. 23. In: Groves HM. The Rate and Direction of Inventive Activity: Economic and

---

85 See Mullin (2013), p. 12

86 See Kleemann (2013), p. 573

87 Biosimilars are subsequent versions of original biopharmaceutical products after patent expiry. Such proteins are more complex and in opposite to a normal generic (small-molecules), they are not a direct copy of the molecule structure. Therefore, the EMA installed a specific market approval process for biosimilars.

88 See Germann *et al.* (2013), p. 2

89 See Gleadle *et al.* (2014), p. 76

Social Factors. Princton: Princeton University Press, 609-626. http://www.nber.org/chapters/c2144 [Accessed: October 5th 2014].

Azoulay P (2002): Do pharmaceutical sales respond to scientific evidence? *Journal of Economics & Management Strategy* 11(4), 551-594. DOI: 10.1111/j.1430-9134.2002.00551.x.

Backhaus J (1983): Competition, innovation and regulation in the pharmaceutical industry. *Managerial and Decision Economics* 4(2), 107-121. DOI: 10.1002/mde.4090040208.

Beishon M (2014): Approval rating: how do the EMA and FDA compare? *CancerWorld* (January-February), 12-17. http://www.cancerworld.org/pdf/9944_pagina_12_17_Cutting_Edge.pdf [Accessed: October 7th 2014].

BfArM [Bundesinstitut für Arzneimittel und Medizinprodukte] (2013): Zulassungsverfahren. Bonn. http://www.bfarm.de/DE/Arzneimittel/zul/zulassungsverfahren/_node.html [Accessed: October 25th 2014].

Breyer F, Zweifel P & Kifmann M (2005): Gesundheitsökonomik. 5th revised Edition. Berlin, Heidelberg, New York: Springer-Verlag. ISBN: 3-540-22816-0.

Cassel D & Ulrich V (2012): Herstellerabgabepreise auf europäischen Arzneimittelmärkten als Erstattungsrahmen in der GKV-Arzneimittelversorgung. [*Gutachten für den Verband Forschender Arzneimittelhersteller e.V. (vfa)*] February 22nd 2012. Berlin. http://www.vfa.de/download/herstellerabgabepreise-auf-europaeischen-arzneimittelmaerkten.pdf [Accessed: October 6th 2014].

Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC & Sculpher M (2015): Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technology Assessment* 19(14). DOI: 10.3310/hta19140.

Crémieux P-Y, Ouellette P & Petit P (2007): Do drugs reduce utilisation of other healthcare resources? *PharmacoEconomics* 25(3), 209-221. ISSN: 1170-7690.

Cutler DM & Kadiyala S (2003): The return to biomedical research: Treatment and behavioral effects. Chapter 4. In: Murphy KM & Topel RH. Measuring the Gains from Medical Research. Chicago, London: The University of Chicago Press, 110-162. ISBN: 0-226-55178-4.

de la Haye R & Gebauer A (2008): Die Entwicklung eines Arzneimittels. Chapter 6. In: Schöffski O, Fricke F-U & Guminski W. Pharmabetriebslehre. Berlin, Heidelberg: Springer, 105-116. ISBN: 978-3-540-79550-6.

DiMasi JA (2008): The Economics of New Drug Development: Costs, Risks, and Returns. [*Presentation*] The New England Drug Metabolism Group Spring Meeting. March 12th 2008. Cambridge, MA. http://www.nedmdg.org/docs/2008/joseph-dimasi-spring-2008.ppt [Accessed: October 9th 2014].

ECORYS (2009): Competitiveness of the EU Market and Industry for Pharmaceuticals - Volume I: Welfare Implications of Regulation. December 2009. Rotterdam: European Commission, Directorate General Enterprise & Industry.

http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/vol_1_welfare_implications_of_regulation_en.pdf [Accessed: October 8th 2014].

EGA [European Generic Medicines Association] (2007): Generic Medicines, Data Exclusivity and Patents. *EGA Fact Sheet on Generic Medicines.* http://www.egagenerics.com/images/factsheet/EGA_factsheet_03.pdf [Accessed: October 1st 2014].

EMA [European Medicines Agency] (2014): Central Authorisation of Medicines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp [Accessed: October 1st 2014].

European Patent Office (2013): Case Law of the Boards of Appael. October 1st 2013. http://www.epo.org/law-practice/legal-texts/html/caselaw/2013/e/clr_i_c_6_2_3_b.htm [Accessed: October 1st 2014].

EvaluatePharma (2014): World Preview 2014, Outlook to 2020. June 2014. Evaluate Ltd. http://www.evaluategroup.com/public/Reports/EvaluatePharma-World-Preview-2014.aspx [Accessed: October 8th 2014].

FDA [Food and Drug Administration] (2014): Novel New Drugs 2013 Summary. January 2014. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM381803.pdf [Accessed: October 8th 2014].

FDA [Food and Drug Administration] (2009): Small Business Assistance: Frequently Asked Questions on the Patent Term Restoration Program. March 31st 2009. http://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069959.htm [Accessed: October 1st 2014].

FRED [Federal Reserve Bank of St. Louis] (2014): Personal Consumption Expenditures: Chain-type Price Index. [*Database*]: U.S. Department of Commerce: Bureau of Economic Analysis. http://research.stlouisfed.org/fred2/series/PCEPI [Accessed: June 5th 2014].

Fricke U (2013): Pharmakologische Bewertungen neuer Arzneimittel 2012. *InVo - Informationen zu Verordnungen in der GKV* April 2013(5), 1-6. http://www.kvwl.de/arzt/verordnung/arzneimittel/info/invo/pharm_bewert_am_2012_invo.pdf [Accessed: August 22nd 2014].

Fricke U (2014): Pharmakologische Bewertungen neuer Arzneimittel 2013. *InVo - Informationen zu Verordnungen in der GKV* Mai 2014(4), 1-7. http://www.kvwl.de/arzt/verordnung/arzneimittel/info/invo/pharm_bewert_am_2013_invo.pdf [Accessed: August 22nd 2014].

Fricke U & Schwabe U (2013): Neue Arzneimittel 2012. 2. In: Schwabe U & Paffrath D. Arzneiverordnungs-Report 2013. Springer Berlin Heidelberg, 47-120. ISBN: 978-3-642-37123-3.

Gagnon M-A & Lexchin J (2008): The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLoS Medicine* 5(1), e1. DOI: 10.1371/journal.pmed.0050001.

Germann PG, Schuhmacher A, Harrison J, Law R, Haug K & Wong G (2013): How to create innovation by building the translation bridge from basic research into medicinal drugs: an industrial perspective. *Hum Genomics* 7, 5. DOI: 10.1186/1479-7364-7-5.

Giaccotto C, Santerre RE & Vernon JA (2005): Drug prices and research and development investment behavior in the pharmaceutical industry. *Journal of Law and Economics* 48(1), 195-214. DOI: 10.1086/426882.

GKV-Spitzenverband (2013): Anzeige einer Anwendungsbeobachtung nach § 67, Abs. 6 AMG oder einer nichtinterventionellen Unbedenklichkeitsprüfung nach § 63f Abs. 4 AMG. July 8th 2013. Berlin. http://www.gkv-spitzenverband.de/krankenversicherung/arzneimittel/anzeige_einer_anwendungsbeobachtung/anzeige_einer_anwendungsbeobachtung.jsp [Accessed: October 1st 2014].

Gleadle P, Parris S, Shipman A & Simonetti R (2014): Restructuring and innovation in pharmaceuticals and biotechs: The impact of financialisation. *Critical Perspectives on Accounting* 25(1), 67-77. DOI: 10.1016/j.cpa.2012.10.003.

Godet V & Ferrand-Nagel S (2002): Medicines in Europe: Scientific convergence and political divergences. *Pharmaceuticals Policy and Law* 5, 107-123. http://iospress.metapress.com/content/79EPVUDF0WDDHP0F [Accessed: October 7th 2014].

Grootendorst P (2009): How should we support pharmaceutical innovation? *Expert Review of Pharmacoeconomics & Outcomes Research* 9(4), 313-320. DOI: 10.1586/erp.09.34.

Guminski W (2008): Produktlebenszyklus und die Möglichkeiten seiner Gestaltung. Chapter 11. In: Schöffski O, Fricke F-U & Guminski W. Pharmabetriebslehre. Berlin, Heidelberg: Springer, 199-213. ISBN: 978-3-540-79550-6.

Hall RE & Jones CI (2007): The value of life and the rise in health spending. *The Quarterly Journal of Economics* 122(1), 39-72. DOI: 10.1162/qjec.122.1.39.

Hancher L (2004): The European community dimension: coordinating divergence. Chapter 3. In: Mossialos E, Walley T & Mrazek M. Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality. *European Observatory on Health Systems and Policies Series*. Maidenhead: Open University Press, 55-81. http://www.euro.who.int/__data/assets/pdf_file/0008/98432/E83015.pdf [Accessed: October 13th 2014].

Hartmann M, Mayer-Nicolai C & Pfaff O (2013): Approval probabilities and regulatory review patterns for anticancer drugs in the European Union. *Critical Reviews in Oncology/Hematology* 87(2), 112-121. DOI: 10.1016/j.critrevonc.2013.01.004.

Häussler B, Gothe H, Reschke P, Höer A, Hagenmeyer E-G, Ryll A & Hempel E (2002): Analog-Wirkstoffe im Arzneimittelmarkt: Therapeutischer Nutzen und

Bedeutung für die Ausgaben der Krankenversicherungen. *Schriftenreihe Strukturforschung im Gesundheitswesen, Bd. 30*. Berlin: IGES-Eigenverlag. ISBN: 3-9808407-1-9. http://www.vfa.de/embed/igesanalogstudie.pdf [Accessed: October 7th 2014].

Häussler B, Höer A, Hempel E & Klein S (2009): Arzneimittel-Atlas 2009: Der Arzneimittelverbrauch in der GKV. München: Urban & Vogel GmbH. ISBN: 978-3899352597.

Helfand C (2013): Top 10 generics makers by 2012 revenue. *FiercePharma.* October 21st 2013. http://www.fiercepharma.com/special-reports/top-10-generics-makers-2012-revenue [Accessed: October 1st 2014].

Hemphill CS & Sampat BN (2012): Evergreening, patent challenges, and effective market life in pharmaceuticals. *Journal of Health Economics* 31(2), 327-339. DOI: 10.1016/j.jhealeco.2012.01.004.

Henderson DR (2010): Regulation Overdose. [*Book Review*] Summer 2010. CATO Institute. http://object.cato.org/sites/cato.org/files/serials/files/regulation/2010/6/regv33n2-9.pdf [Accessed: October 7th 2014].

Hernández H, Tübke A, Hervás F, Vezzani A, Amoroso S & Dosso M (2013): The 2013 EU Industrial R&D Investment Scoreboard. *Scientific and Technical Research series.* Luxembourg: European Commission. DOI: 10.2791/26181.

Howard P & Feyman Y (2014): If A Drug Is Good Enough for Europeans, It's Good Enough for Us. [*Blog*] February 14th 2014. Health Affairs. http://healthaffairs.org/blog/2014/02/14/if-a-drug-is-good-enough-for-europeans-its-good-enough-for-us/ [Accessed: October 1st 2014].

Howie LJ, Hirsch BR & Abernethy AP (2013): A comparison of FDA and EMA drug approval: implications for drug development and cost of care. *Oncology (Williston Park, N.Y.)* 27(12), 1195-1202. http://www.cancernetwork.com/oncology-journal/comparison-fda-and-ema-drug-approval-implications-drug-development-and-cost-care [Accessed: October 7th 2014].

IMF [International Monetary Fund] (2014): IMF Data Mapper - World Economic Outlook - GDP based on PPP. [*Database*]. http://www.imf.org/external/datamapper/index.php [Accessed: September 11th 2014].

Institut der deutschen Wirtschaft (2013): Die Pharmazeutische Industrie in Deutschland - Ein Branchenportrait. 2nd revised Edition. Köln: Verband Forschender Arzneimittelhersteller (vfa). http://www.vfa.de/download/branchenportrait.pdf [Accessed: October 8th 2014].

Jacob R (2008): Patents and Pharmaceuticals. [*Presentation*] Public presentation of preliminary findings - Report of the Pharma-sector inquiry. November 29th 2008. Brussels. http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/jacob.pdf [Accessed: October 7th 2014].

Jena AB & Philipson TJ (2007): Cost-effectiveness as a price control. *Health Affairs* 26(3), 696-703. DOI: 10.1377/hlthaff.26.3.696.

Jensen MC (1986): Agency Costs of Free Cash Flow, Corporate Finance, and Takeovers. *American Economic Review* 76(2), 323. ISSN: 00028282.

Kaber G & Twarock S (2009): Beurteilungsverfahren neuer Arzneimittel - Eine kritische Bewertung. *Fortbildungstelegramm Pharmazie* 3(Juni/Juli), 145-161. http://www.uni-duesseldorf.de/kojda-pharmalehrbuch/Fortbildungstelegramm Pharmazie/FTP_Juni_Juli_2009_Uebersicht.pdf [Accessed: October 9th 2014].

Kaitin KI & DiMasi JA (2011): Pharmaceutical innovation in the 21st Century: New Drug Approvals in the first decade, 2000-2009. *Clinical Pharmacology and Therapeutics* 89(2), 183-188. DOI: 10.1038/clpt.2010.286.

Kanavos P (2014): Measuring performance in off-patent drug markets: A methodological framework and empirical evidence from twelve EU Member States. *Health Policy* 118(2), 229-241. DOI: 10.1016/j.healthpol.2014.08.005.

Kesselheim A, Wang B & Avorn J (2013): Defining "innovativeness" in drug development: A systematic review. *Clinical Pharmacology and Therapeutics* 94(3), 336-348. DOI: 10.1038/clpt.2013.115.

Kleemann A (2013): Metamorphosis of the pharmaceutical industry. *Pharmazeutische Industrie* 75(4), 562-574.

Kornfield R, Donohue J, Berndt ER & Alexander GC (2013): Promotion of prescription drugs to consumers and providers, 2001–2010. *PloS One* 8(3), e55504. DOI: 10.1371/journal.pone.0055504.

Kremer M (1998): Patent buyouts: A mechanism for encouraging innovation. *The Quarterly Journal of Economics* 113(4), 1137-1167. DOI: 10.1162/003355398555865.

Lehmann B (2003): The Pharmaceutical Industry and the Patent System. President, International Intellectual Property Institute. http://users.wfu.edu/mcfallta/DIR0/pharma_patents.pdf [Accessed: October 9th 2014].

Lichtenberg FR (2005): The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982–2001. *International Journal of Health Care Finance and Economics* 5(1), 47-73. DOI: 10.1007/s10754-005-6601-7.

Lichtenberg FR (2007): Importation and innovation. *Economics of Innovation and New Technology* 16(6), 403-417. DOI: 10.1080/10438590601002307.

Light DW & Lexchin JR (2012): Pharmaceutical research and development: what do we get for all that money? *British Medical Journal* 345, e4348. DOI: 10.1136/bmj.e4348.

Lilly Pharma (2013): Entwicklungsstufen eines neuen Medikaments. November 18th 2013. Bad Homburg. http://www.lilly-pharma.de/unternehmen/forschung/entwicklungsstufen-eines-neuen-medikaments.html [Accessed: October 2nd 2014].

Lowe D (2013): But Don't Drug Companies Spend More on Marketing? [*Blog*] May 20th 2013. Corante. http://pipeline.corante.com/archives/2013/05/20/

but_dont_drug_companies_spend_more_on_marketing.php [Accessed: October 5th 2014].

Mahan D (2002): Profiting from Pain: Where Prescription Drug Dollars Go. July 2002. (No. 02-105). Washington, DC: Families USA. http://research.policyarchive.org/6305.pdf [Accessed: October 8th 2014].

Mestre-Ferrándiz J, Sussex J & Towse A (2012): The R&D Cost of a New Medicine. London: Office of Health Economics. ISBN: 978-1-899040-19-3.

Montalban M & Sakinç ME (2013): Financialization and productive models in the pharmaceutical industry. *Industrial and Corporate Change* 22(4), 981-1030. DOI: 10.1093/icc/dtt023.

Mullin R (2013): The future is now. [*Cover Story*] *Chemical and Engineering News* 91(49), 12-17. http://cen.acs.org/content/dam/cen/91/49/09149-cover.pdf [Accessed: October 7th 2014].

Nair HS, Manchanda P & Bhatia T (2010): Asymmetric social interactions in physician prescription behavior: the role of opinion leaders. *Journal of Marketing Research* 47(5), 883-895. DOI: 10.1509/jmkr.47.5.883.

Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR & Schacht AL (2010): How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery* 9(3), 203-214. DOI: 10.1038/nrd3078.

PhRMA [Pharmaceutical Research and Manufacturers of America] (2014): 2014 Biopharmaceutical Research Industry Profile. April 2014. Washington, DC. http://www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf [Accessed: October 9th 2014].

PhRMA [Pharmaceutical Research and Manufacturers of America] (ed.) (2007): Drug Discovery and Development: Understanding the R&D Process. February 2007. Washington, DC. http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf [Accessed: October 9th 2014].

PhRMA [Pharmaceutical Research and Manufacturers of America] (2012): Pharmaceutical Industry Profile 2012. April 2012. Washington, DC. http://www.phrma.org/sites/default/files/pdf/phrma_industry_profile.pdf [Accessed: October 9th 2014].

Putzeist M, de Jong JP, Stolk P & Consultancy E (2013): Background Paper 8.2 Regulatory Structures to Support Pharmaceutical Innovation. *Priority Medicines for Europe and the World "A Public Health Approach to Innovation"*. http://www.who.int/medicines/areas/priority_medicines/BP8_2regulatory.pdf [Accessed: August 19th 2015].

Raasch A-C (2006): Der Patentauslauf von Pharmazeutika als Herausforderung beim Management des Produktlebenzyklus. Wiesbaden: Deutscher Universitäts-Verlag. ISBN: 978-3-8350-0632-4.

Raasch A-C & Schöffski O (2008): Management des Patentauslaufs. Chapter 12. In: Schöffski O, Fricke F-U & Guminski W. Pharmabetriebslehre. Berlin, Heidelberg: Springer, 215-231. ISBN: 978-3-540-79550-6.

Ranbaxy Laboratories (2012): Ranbaxy Launches Synriaum - India's First New Drug. [*Press Release*] April 25th 2012. http://www.ranbaxy.com/ranbaxy-launches-synriam-indias-first-new-drug/ [Accessed: October 5th 2014].

Ross DB (2007): Overdose: How excessive government regulation stifles pharmaceutical innovation. [*Book Review*] *The Journal of Clinical Investigation* 117(12), 3598-3598. DOI: 10.1172/JCI33611.

Scannell JW, Blanckley A, Boldon H & Warrington B (2012): Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery* 11(3), 191-200. DOI: 10.1038/nrd3681.

Schacht WH & Thomas JR (2002): Pharmaceutical Patent Term Extensions: A Brief Explanation. (RS21129). *CRS Report for Congress.* United States Congressional Research Service. http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RS21129.pdf [Accessed: October 7th 2014].

Schamp K, Regenold J & Jordan H (2008): Regulatory Affairs. Chapter 8. In: Schöffski O, Fricke F-U & Guminski W. Pharmabetriebslehre. Berlin, Heidelberg: Springer, 129-153. ISBN: 978-3-540-79550-6.

Schnee JE (1979): Regulation and innovation: U.S. pharmaceutical industry. *California Management Review* 22(1), 23-32. ISSN: 0008-1256.

Sozialpolitischer Arbeitskreis Berlin (Sab) (1971a): Forschung in der Pharmaindustrie und Marktmonopole. *Sab-Archiv.*

Sozialpolitischer Arbeitskreis Berlin (Sab) (1971b): Materialien zur Forschungssituation und -Politik der Pharmazeutischen Industrie. *Sab-Archiv.*

Spitz J & Wickham M (2012): Pharmaceutical high profits: the value of R&D, or oligopolistic rents? *American Journal of Economics and Sociology* 71(1), 1-36. DOI: 10.1111/j.1536-7150.2011.00820.x.

Statistisches Bundesamt (ed.) (2015): Volkswirtschaftliche Gesamtrechnungen - Inlandsproduktberechnung - Fachserie 18 Reihe 1.4 - 2014. Wiesbaden.

Taylor L (2010): US patients "should have EU-approved drugs". *Pharma Times.* July 28th 2010. http://www.pharmatimes.com/Article/10-07-28/US_patients_%E2%80%9Cshould_have_EU-approved_drugs%E2%80%9D.aspx [Accessed: September 12th 2015].

Trotta F, Leufkens HGM, Schellens JHM, Laing R & Tafuri G (2011): Evaluation of oncology drugs at the European medicines agency and US Food and Drug Administration: When differences have an impact on clinical practice. *Journal of Clinical Oncology* 29(16), 2266-2272. DOI: 10.1200/jco.2010.34.1248.

UNICEF (2013): The Advance Market Commitment for Pneumococcal Vaccine. May 14th 2014. New York, NY. http://www.unicef.org/supply/index_60990.html [Accessed: October 5th 2014].

Venkataraman S & Stremersch S (2007): The debate on influencing doctors' decisions: Are drug characteristics the missing link? *Management Science* 53(11), 1688-1701. DOI: 10.1287/mnsc.1070.0718.

vfa [Verband Forschender Arzneimittelhersteller] (2013): Statistics 2013 - Die Arzneimittelindustrie in Deutschland. September 2013. Berlin. http://www.vfa.de/download/statistics-2013.pdf [Accessed: October 8th 2014].

Virts JR & Weston JF (1980): Returns to research and development in the US pharmaceutical industry. *Managerial and Decision Economics* 1(3), 103-111. DOI: 10.1002/mde.4090010302.

Vogler S, Zimmermann N, Leopold C & de Joncheere K (2011): Pharmaceutical policies in European countries in response to the global financial crisis. *Southern Med Review* 4(2), 22-32. http://apps.who.int/medicinedocs/documents/s19046en/s19046en.pdf [Accessed: October 7th 2014].

Weiss D, Naik P & Weiss R (2009): The 'big pharma' dilemma: develop new drugs or promote existing ones? *Nature Reviews Drug Discovery* 8(7), 533-534. DOI: 10.1038/nrd2923.

Westermark K (2007): The regulation of orphan medicines in the EU: Objectives reached and main challenges when facing the future. *Pharmaceuticals Policy and Law* 9(3), 327-342.

WHO [World Health Organization]. (1948): Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. April 7th 1948. New York, NY. http://www.who.int/about/definition/en/print.html [Accessed: October 5th 2014].

Yardeni E & Abbott J (2014): S&P 500 Sectores & Industries Profit Margins. October 6th 2014. Yardeni Research. http://www.yardeni.com/pub/sp500margin.pdf [Accessed: October 7th 2014].

VI. Consequences of the Early Benefit Evaluation in Germany on the innovational behavior of the pharmaceutical industry

VI.1 Introduction

National health systems are often under strong legislative control.[1] The market for pharmaceuticals is no exception. In most countries the producers of pharmaceutical products cannot set the prices for their products without restrictions. In a regulatory process, agencies and boards decide or negotiate prices and reimbursement limits.[2]

In general, regulation takes into account the competitive environment in the pharmaceutical market. Basically two fundamental types can be distinguished. Firstly, there is the market for pharmaceuticals under patent protection. These products have a temporary monopoly for an active ingredient and regulators often try to find a balance between an (allowed) monopoly rent of the manufacturer and a goal of efficiency and fairness in the national health system. Secondly, there is the market for generics. With the end of a patent, other manufacturers can copy the original product and launch so-called generics. In this case, regulation tries to ensure competition in the market. On the one hand, the original product should face competition thorough fast and easy market entry. On the other hand, the different generic products should be handled as perfect substitutes by stakeholders. Generic manufacturers should not be able to gain market power through branding. Before 2011, market regulation in Germany focused on the

---

1 International institutions like the European Observatory of the WHO provide broad overviews about different national health systems: http://www.euro.who.int/en/-about-us/partners/observatory/health-systems-in-transition-hit-series/countries-and-subregions

2 See Sood *et al.* (2009)

second type.[3] With the Act on the Reform of the Market for Medicinal Products (*Arzneimittelmarktneuordnungsgesetz,* AMNOG) the legislator introduced the so-called early benefit evaluation (*frühe Nutzenbewertung,* fNB). It changed dramatically the patent market. The following paper analyzes the effect by the reform on the investment decision of pharmaceutical firms.

Before 2011, patent drugs only faced limited direct regulation. New drugs were (and still are) automatically reimbursable with market approval and producers were able to set their list prices freely.[4] Restrictions regarding reimbursement were only possible after product launch. In addition, the manufacturer had his local monopoly through his patent. Market power countervailing on the demand side had been low, because the roles of demander, consumer and payer were separated. The physician prescribed the active ingredient (and the pharmacist dispenses the exact product), the patient consumed the products and the sickness fund paid for it. Therefore, the price elasticity of physicians and patients was relatively low.[5] They bared the cost either only indirectly (prescription budgets for physicians) or only for a small part (co-payments by the patients). The direct reimbursement of the list price was criticized claiming how it led to wrong incentives in terms of research and innovation. In an attempt to minimize their risk of failed research projects, pharmaceutical companies would not invest in real innovations with a new mode of action and a significant improvement for therapy. Instead, the focus would be on chemical variations ("me-toos") of existing products with only a small additional benefit compared to the established product.[6] These circumstances led to the accusation that the list prices of patent

---

3 See Busse & Blümel (2014) for a comprehensive view of the German health care system.

4 See Paris & Belloni (2013)

5 See Lichtenberg (2007)

6 See Croghan & Pittman (2004)

drugs were often too high because of underdeveloped competition and did not represent their medical benefit.[7]

The early benefit evaluation was introduced on January 1st 2011.[8] New drugs are still automatically reimbursable, but free pricing is limited to the first year. Nearly every new molecular entity (NME) launched in the German drug market has to go through it. An exception exists only for NMEs with an expected revenue in the outpatient sector of less than one million euro per year. The Federal Joint Committee (*Gemeinsamer Bundesausschuss,* G-BA) is responsible for the evaluation. The G-BA is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany.[9] When a new entity enters the market, the G-BA assesses within six months (three months for evaluation and three months for the hearing) whether a claimed additional benefit in relation to an "appropriate comparator" (*zweckmäßige Vergleichstherapie,* ZVT) exists. For this purpose, the company submits a dossier to the G-BA based on the authorization documents and all studies carried out on the pharmaceutical.[10] The producer has to prove the additional benefit of the drug in comparison to at least one ZVT (the total number depends on the number of defined subgroups) set forth by the G-BA. The evaluation is based on the international criteria of evidenced based medicine (EBM). The extent of the additional benefit is not reported as a specific value but as one of six verbal categories, ranging from "less" (less benefit than the ZVT) to "major" (sustained and large improvement compared to the ZVT). The G-BA also reports its certainty about the results, ranging from "not stated" to "proof". Based on these results and on price information from other European countries, the pharmaceutical manufacturer and the Federal Association of Statutory Sickness Funds (*GKV-Spitzenverband*) negotiate the reimbursement price. The negotiation

---

7 See Schlette & Hess (2013)

8 In German: *frühe Nutzenbewertung* (see §35a SGB V and also section II.1.2)

9 See G-BA (2014)

10 See Schlette & Hess (2013)

process can take up to six months leading to a total of about one year to settle the negotiated price. During that time, the drug is reimbursable under its original price. If the parties cannot find an agreement, an arbitration body decides within three months.[11] The decision of the body applies retroactively to the end of the one year period.

The sections analyzing the early benefit evaluation are structured as followed. Section VI.2 gives a short review about existing theoretical literature that discusses investment decisions of pharmaceutical firms. Section VI.3 introduces the model. In Section VI.4 it is discussed how the benefit of a drug is observed and how this affects the profits of the firm. In a second step (Section VI.5), the influences on the investment decisions of the pharmaceutical firms are elaborated. In Section VI.6 the theoretical results are controlled through a numerical approach based on conducted early benefit evaluations. Section VI.7 discusses the results and Section VI.8 concludes the paper.

VI.2 Literature Review

A basic result of market regulation is the diminishing effect on profits and therefore on the output of new products.[12] But a regulator would question if the products not produced were even "worth" being developed and if the money would have been better spent in other areas of the health care system. Under- and over-research is possible in regard of social welfare.[13] As a consequence, property rights regulation and pharmaco-economic evaluation try to achieve a socially acceptable optimum in research. There exists a comprehensive literature discussing the arrangement and extent of patents.[14] The concept of pharmaco-economic approaches to evaluate the benefit of drugs is also profoundly

---

[11] See ibid.

[12] See Giaccotto *et al.* (2005) and Lichtenberg (2007)

[13] See Arvidsson (1970)

[14] See for example Acemoglu & Akcigit (2006), Grinols & Henderson (2007) and Saint-Paul (2004)

elaborated[15] and widely discussed.[16] However in the analysis of this paper, the matter of interest is the link between the investment decision and the regulative instrument of value-based pricing. Some microeconomic market models analyzing this relationship shall be presented here.

When it comes to the market analyses, a basic question is the trade-off between static and dynamic efficiency, that is to say, the pricing of a product entering the market or the change of the innovation process in the future.[17] There is strong concern that legislators focus shortsightedly on static efficiency to ensure efficient treatment for current patients but do not consider the disadvantage for future patients because of reduced R&D activities. This aspect is often discussed in the following papers.

The paper of Chao and Kavadias (2008) focuses on the strategic organization of the research process and does not differentiate regulative environments but its basic framework is comparable to the model analyzed later in the paper. The authors also distinguish between different types of innovation (radical and incremental) based on probability of success (lower for radical innovation), potential performance (higher for radical innovation) and cost (higher for radical innovation). Regarding the characteristics of the product, their model is more complex. Innovation is seen by Chao and Kavadias as the improvement of an existing product and the product has a defined number of attributes that can be altered. As a result, the radical innovation is preferred in the long run but market disruptions (and the introduction of an early benefit evaluation could be seen as one) make it more likely for firms to thrive for shorter time horizons for new products and will prefer incremental improvements. This emphasizes the importance of predictability regarding market regulation.

---

15 See for example Drummond *et al.* (2005), Hurley (2000) and Kleijnen *et al.* (2011)

16 See for example Atun & Gurol-Urganci (2007), Chalkidou *et al.* (2009) and Claxton *et al.* (2000)

17 See Kanavos *et al.* (2010)

The most prominent pharmaco-economic approach is the cost-effectiveness analysis (CEA). It values new medical products on the ratio of additional cost to additional benefit compared to an alternative therapy. When the calculated incremental cost-effectiveness ratio (ICER) remains under a defined threshold, the new therapy is seen as effective and reimbursable.[18] The English National Institute for Health and Care Excellence (NICE) is the most noted agency for such an analysis.[19] Vernon *et al.* (2005) describe how a pharmaceutical company can take the ICER into account to determine what maximum price a pharmaceutical can set to remain under the threshold or the probability to remain under the limit for a specific price. The consequences of over- and underinvestment through thresholds differing from the socially desirable level are discussed more deeply in Vernon *et al.* (2009). The authors also emphasize additional effects (price signal as incentive for future research, spillover effects through research) that are not reflected in the ICER.

Jena and Philipson (2008) also investigate the influence of a threshold on the dynamic efficiency of research and development. They take a stronger focus on total welfare. In their model the benefit from the innovation is given. The probability for a specific innovation increases with the amount of money spent for R&D. This differs from the model discussed later where the amount spent is given but the benefit is random. They point out that in a static economy, social welfare would be maximized with prices equal to marginal cost but this would eliminate any future research. That is why the company must receive some share of the consumer surplus. Cost-effectiveness thresholds should therefore consider the social value of an innovation. The authors emphasize the difference between cost-efficiency (ratio of benefit and cost) and economic efficiency (difference between

---

[18] Schad & John (2012)

[19] More precisely, the NICE conducts a cost-utility analysis (CUA) because it consolidates different outcomes into one entity. The benefit is expressed in Quality Adjusted Life Years (QALY).

benefits and cost). Even though an increase in the benefit level raises both values, a cost-effective output must not be on an efficient economic level.[20]

Friederiszick *et al.* (2009) investigate the influence of internal and external reference pricing on the portfolio management of pharmaceutical firms and the interaction between the different regimes. As described in the introduction, the arbitration board of the German early benefit evaluation is obliged to consider European prices (external reference pricing). The authors here define a drug as highly innovative when it is the first mover in the market making the degree of innovation relative. The regulators hope to encourage innovation through price premiums for highly innovative products. This goal is not achieved according to the analysis of Friederiszick *et al.* (2009). Through dynamic programming the authors show that there is a slight shift in the research portfolio. Fewer projects are started because of reduced sales expectations, and the share of highly innovative projects decreases because firms fear to loose the status of being highly innovative when other products reach market approval first.

Ganuza *et al.* (2009) do not mention cost-effectiveness analysis explicitly but their model uses a similar theoretical approach by considering a linear utility function of the patient and a normalized profit function. The investment process is random and more effort increases the chance for a higher benefit. Their static market model assumes that all physicians observe the benefit of a drug and a fraction of them has a price sensitive demand like the regulator has under the German early benefit evaluation. The higher the share of price sensitive doctors the higher the incentive for high innovations. Through marketing the pharmaceutical firm is able to induce additional benefit and the marketing can work to some extent as a substitute for efforts in research. In a related working paper they emphasize that in the oligopolistic case, the results are ambiguous because in a "winner-takes-all tournament" even overinvestment is possible.[21]

---

[20] See Philipson & Jena (2006)

[21] See Ganuza *et al.* (2007)

The literature discussed gives an interesting insight on how the economic evaluation of pharmaceuticals changes the incentives in the market and it emphasizes that legislators moves on a narrow path between encouraging and discouraging innovation. In regard to CEA, the determination of the ICER threshold is the crucial factor. In the papers presented here, the threshold remains a political factor that cannot be objectified in the end. But there are indications that current thresholds are too low because they focus too much on the specific cost of the health care system and do not consider external and dynamic effects.[22] Technically, the early benefit evaluation is not a CEA and does not define a threshold. The responsible authorities even try to distance themselves from such methods.[23] But the following sections will show that in the end they have to follow a similar logic.

VI.3 The Model

A manufacturer for pharmaceuticals faces the decision to enter a market for a specific indication. If he does, he will compete with the existing product, the appropriate comparator (ZVT) in the market.

It is assumed that the patient either receives one unit of the new drug or the ZVT. Information about the prevalence and incidence of a disease allow an estimation about the expected number of patients respectively consumers.[24] Hence, the consumed amount can be seen as constant and normalized to one. The analysis can therefore be reduced to the point of view of one patient and his additional benefit from the drug compared to the cost.

The benefit of a drug can be separated into two parts. Firstly, the medical benefit Q sums all positive and negative effects of a drug that can be measured by the

---

22 See Jena & Philipson (2007)

23 See Breyer (2010)

24 See Messori *et al.* (2010)

methods of evidence based medicine.[25] When $Q \geq 0$ the drug will receive market authorization from the responsible agency and can be brought into the market. Secondly, the "subjective" benefit q is not comprehensible by evidence based medicine even though it can be therapeutically and medically relevant. This benefit can be subjective but mainly it will be seen here as the benefit induced by the manufacturer through marketing techniques and will be equal for all physicians and patients. Market authorities and regulators normally do not consider q. Although the medical benefit Q can be positive or negative, the subjective benefit is $q \geq 0$ since it is obvious that the manufacturer would not try to diminish the benefit of its product.

The price per unit of the product is expressed as p. The physicians consider the price of the product even though they do not bear it, because nearly every office-based physician faces a budget limit for his prescriptions. He might faces financial claims if he can not prove that his prescriptions fulfill the general efficiency demand (services should be adequate, sufficient and efficient) of the German health care system.[26] The difference between the benefits of the drug and its price is the net benefit V.

The index 0 denotes the existing product in the market. It is assumed that $q_0 = 0$. Because of the long experience with the product in the market, only the evidence based benefit plays a role and the manufacturers are not able to induce a subjective benefit into the product. The net benefit of the consumer from the appropriate comparator can therefore be written as

$$V_0 = Q_0 - p_0 \tag{1}$$

In regard to the new drug the net benefit V is defined as

$$V = Q + q - p \tag{2}$$

[25] This is also the principle for the German early benefit evaluation (see IQWiG (2013), p. 6)

[26] See KBV (2014)

It is assumed that the physicians will choose the new drug when they are at least indifferent between the two products. From setting $V_0 = V$, the maximum price of the new product can be described as

$$p = \max\{0, p_0 + Q + q - Q_0\} \quad (3)$$

Note that the manufacturer will only bring his product to the market when he can achieve a strictly positive price. Considering equation (1), the price can also be written as

$$p = \max\{0, Q + q - V_0\} \quad (4)$$

As the quantity sold equals one, firm's profit is given by

$$\Pi = p - c \quad (5)$$

Using equation (4) to replace price p, the profit can be written as

$$\Pi = \max\{-c, Q + q - V_0 - c\} \quad (6)$$

The cost c are the average cost per unit and patient because the manufacturer can estimate the prevalence of the disease and the number of eligible patients receiving the product.[27] For the ZVT, it is assumed that the patent has expired and different manufacturers of generics compete on the market in perfect competition. Former R&D costs of the comparator were refinanced in its patent phase and do not play a role here anymore. Therefore, it holds that price is equal to average cost, $p_0 = c_0$. This also excludes price reactions of the market incumbents to the price setting of the new product. This does not necessarily mean that the incumbents have to leave the market, since established products often have a wider therapeutic bandwidth than new products at market entree.

The new product is assumed to have higher average cost $c \geq c_0$, as the manufacturer has to refinance research and development. From the firm's point of view, the R&D costs are fixed. It has to bear them, even if the product is not sold.

[27] See Häussler (2013), p. 17

The variable costs on the other side are relatively small so that c can be seen as completely fixed, whether the product is sold or not (see equation (6))

The medical evidence based benefit Q is the result of a research process with unknown outcome. The way pharmaceutical research is done shows that it is upfront relatively unknown what drug will reach market approval and what its characteristics will be.[28] It is assumed that all market participants are risk neutral. Following from equation (5), the firm has an expected profit of

$$E(\Pi) = E(p) - c \qquad (7)$$

The probability of the achieved benefit can be expressed with a density function $f(Q)$. It shall be assumed that the sample space Ω for the possible value Q has an upper limit Q_b and a lower limit Q_a. From a medical point of view the upper limit could be seen as immediate cure and respectively the lower limit as painful death. Hence, the sample space is $\Omega = [Q_a, Q_b]$. It is assumed that for the lower limit $Q_a < 0$. For the evidence based medical benefit Q_0 of the ZVT it holds $0 < Q_0 < Q_b$. A utility $Q = 0$ expresses the minimum medical benefit that the new product needs in order to be granted market approval by the responsible agency.

VI.4 Firm's profit under complete and incomplete information

Two scenarios will be distinguished hereafter. Physicians can observe the outcome of the research process in the first scenario (complete information) but they cannot in the second one (incomplete information).

VI.4.1 Expected profits under complete information

Under complete information the physicians can observe the medical benefit Q and the subjective benefit q of the new drug. As stated in equation (4), the manufacturer will launch his product on the market when he can offer it for a

[28] See Stonebraker (2002)

positive price p. Consequently, there is a lower limit for the medical benefit for which this is possible. Based on equation (4), it must hold for the medical benefit

$$Q \geq V_0 - q \tag{8}$$

But as remarked before, the manufacturer will only receive market approval when his medical utility is $Q \geq 0$. Consequently, two cases, $V_0 - q < 0$ and $V_0 - q \geq 0$, must be distinguished. In the following an index v indicates a profit under complete information and the expected profit follows from equation (7) as

$$E(\Pi^v) = \int_{\max\{0;V_0-q\}}^{Q_b} (Q + q - V_0) * f(Q)\,\mathrm{d}Q - c \tag{9}$$

The integral can be interpreted as $\int_{\max(0;V_0-q)}^{Q_b} \omega * \nu'$ with $\omega = Q + q - V_0$ and $\nu = F(Q) = \bar{F}'(Q)$, where $F(Q)$ is the cumulative distribution function of the density function $f(Q)$ and the first derivate of the function $\bar{F}(Q)$. The latter can be taken as the area under the distribution function.[29] According to the technique of partial integration the integral can be written as

$$\int_{\max\{0;V_0-q\}}^{Q_b} \omega * \nu' = [\omega * \nu]_{\max(0;V_0-q)}^{Q_b} - \int_{\max\{0;V_0-q\}}^{Q_b} \omega' * \nu \tag{10}$$

Therefore, equation (9) can be written for case $V_0 - q \geq 0$ as

$$\begin{aligned} E(\Pi^v) &= [F(Q) * \omega]_{V_0-q}^{Q_b} - \int_{V_0-q}^{Q_b} \mathrm{F}(Q) * \omega'\,\mathrm{d}Q - c \\ &= F(Q_b)(Q_b + q - V_0) - \left(\bar{F}(Q_b) - \bar{F}(V_0 - q)\right) - c \\ &= Q_b - (V_0 - q) - \left(\bar{F}(Q_b) - \bar{F}(V_0 - q)\right) - c \end{aligned} \tag{11}$$

Thereby it was taken into account that $\omega' = 1$. Furthermore, it was considered that for the distribution function it holds $F(Q_a) = 0$ and $F(Q_b) = 1$.

In case of $V_0 - q < 0$, the expected profit is

---

[29] Formally: $\bar{F}(x) = \int_{-\infty}^{x} F(Q)\,\mathrm{d}Q = \int_{Q_a}^{x} F(Q)\,\mathrm{d}Q$. For values $Q < Q_a$ the probability of occurrence is zero and therefore the area under the distribution function as well.

$$\begin{aligned} E(\Pi^v) &= [F(Q) * \omega]_0^{Q_b} - \int_0^{Q_b} F(Q) * \omega' \, dQ - c \\ &= F(Q_b)(Q_b + q - V_0) - F(0)(q - V_0) - \left(\bar{F}(Q_b) - \bar{F}(0)\right) - c \\ &= Q_b - \left(1 - F(0)\right)(V_0 - q) - \left(\bar{F}(Q_b) - \bar{F}(0)\right) - c \end{aligned} \tag{12}$$

VI.4.2 Expected profit under incomplete information

In the second scenario it is assumed that the physicians cannot observe the specific benefit Q of the new drug but they take assumptions about its benefit based on their experience about other drugs in the market. The benefit Q_0 of the appropriate comparator remains known to the physicians because of their long experience with the drug.

The benefit of the new drug is not observable because the mandate of the market agencies is not to verify the full evidence based medical benefit of a drug but only its safety, quality and efficacy.[30] Drugs for the treatment of hypertension are an example. They are efficient when they can reduce the blood pressure, but their medical benefit is the prevention of heart attacks.[31] It is also assumed that the manufacturer himself is not able to show credibly the benefit of his drug, since he has an incentive to exaggerate the positive characteristics of his product.

It is assumed that the physicians (patients) are risk neutral in their prescription decision. The physicians can only observe products that receive market approval ($Q \geq 0$). Thus, their expectations about the benefit of a new drug is biased and the maximum price $\bar{p}$ they are willing to pay is defined by $V_0 = E(V|Q \geq 0 \wedge p = \bar{p})$.[32] By equation (2), the condition is equivalent to $V_0 = E(Q|Q \geq 0\,) + q - \bar{p}$, respectively

$$\bar{p} = E(Q|Q \geq 0\,) + q - V_0 \tag{13}$$

---

30 See Vernon *et al.* (2005)

31 See Thürmann (2013), p. 110

32 Recall that q is not stochastic.

In order to maximize expected profits the manufacturer will set this maximum price when it is positive. If $\bar{p} \leq 0$, he will set price 0 and effectively not enter the market. It holds

$$E(p|Q \geq 0\,) = \max\{0, \bar{p}\} \tag{14}$$

Using equation (7), the expected profit under incomplete information (indexed by u) is

$$\begin{aligned} E(\Pi^u) &= \int_0^{Q_b} E(p|Q \geq 0\,) * f(Q)\,\mathrm{d}Q - c \\ &= \max\{0, \bar{p}\} \int_0^{Q_b} f(Q)\,\mathrm{d}Q - c \\ &= \max\{0, \bar{p}\}\big(1 - F(0)\big) - c \end{aligned} \tag{15}$$

Note that $E(p|Q \geq 0\,)$ can be moved in front of the integral because the expected conditional benefit $E(Q|Q \geq 0\,)$ is a constant. As stated above for $\bar{p} \leq 0$, the company will not enter the market and the expected profit is

$$E(\Pi^u) = 0 * \big(1 - F(0)\big) - c = -c \tag{16}$$

When $\bar{p} > 0$, it follows from equation (13) that the expected profit can be written as

$$\begin{aligned} E(\Pi^u) &= \bar{p}\big(1 - F(0)\big) - c \\ &= [E(Q|Q \geq 0\,) + q - V_0]\big(1 - F(0)\big) - c \end{aligned} \tag{17}$$

For deriving the expected benefit $E(Q|Q \geq 0\,)$, it must be considered that the manufacturer takes the observation bias of the physicians into account. The conditional probability density for the expected benefits is

$$f(Q|Q \geq 0) = \frac{f(Q)}{\int_0^{Q_b} f(Q)\,\mathrm{d}Q} = \frac{f(Q)}{1 - F(0)} \tag{18}$$

This leads to the following expected benefit

$$E(Q|Q \geq 0) = \int_0^{Q_b} Q * f(Q|Q \geq 0)\,\mathrm{d}Q$$

$$
\begin{aligned}
&= \frac{1}{1-F(0)} \int_0^{\mathrm{Q_b}} Q * f(Q)\,\mathrm{d}Q \\
&= \frac{1}{1-F(0)} \left[[Q * F(Q)]_0^{\mathrm{Q_b}} - \int_0^{\mathrm{Q_b}} F(Q)\,\mathrm{d}Q \right] \\
&= \frac{1}{1-F(0)} [\mathrm{Q_b} - \bar{F}(Q_b) + \bar{F}(0)]
\end{aligned}
\tag{19}
$$

where again the rule of partial integration has been used. Inserting (19) into (17) yields to

$$
\begin{aligned}
E(\Pi^u) &= \left[\frac{1}{1-F(0)} [Q_b - \bar{F}(Q_b) + \bar{F}(0)] + q - V_0 \right] \big(1 - F(0)\big) - c \\
&= Q_b - \big(1 - F(0)\big)(V_0 - q) - \big(\bar{F}(Q_b) - \bar{F}(0)\big) - c
\end{aligned}
\tag{20}
$$

VI.4.3 Comparison of expected profits under complete and incomplete information

The following section compares what regime the manufacturer would prefer if he could choose between complete and incomplete information. Based on the previous results the following lemma can be stated.

Lemma 1: From the point of view of the manufacturer a regime under complete information is never worse than a regime under incomplete information.

Proof: It must be shown that for the differences of the expected profits it holds $E(\Pi^u) - E(\Pi^v) \leq 0$.

First it is assumed $\bar{p} \leq 0$. In this case the expected benefit $E(Q|Q \geq 0)$ under incomplete information is so low that the expected profit is $E(\Pi^u) = -c$ (see equation (16)). Obviously the expected profit $E(\Pi^v)$ under complete information given by (11) and (12) can never be lower than that.

In the following it is assumed $\bar{p} > 0$. In case of $V_0 - q \geq 0$ the differences between the expected profits under incomplete (20) and complete (11) information is

$$
\begin{aligned}
E(\Pi^u) - E(\Pi^v) &= Q_b - \big(1 - F(0)\big)(V_0 - q) - \big(\bar{F}(Q_b) - \bar{F}(0)\big) - c \\
&\quad - \big(Q_b - (V_0 - q) - \big(\bar{F}(Q_b) - \bar{F}(V_0 - q)\big) - c\big) \\
&= F(0)(V_0 - q) - \big(\bar{F}(V_0 - q) - \bar{F}(0)\big)
\end{aligned} \tag{21}
$$

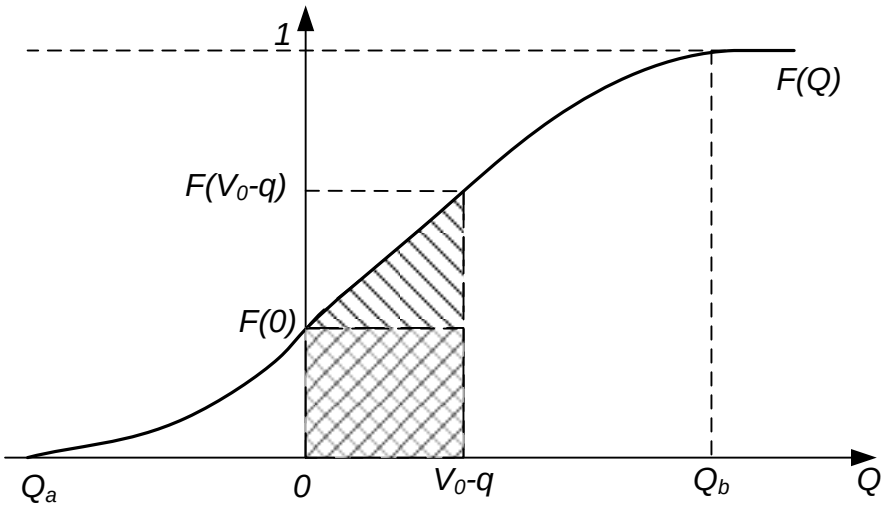
As already described, $\bar{F}(Q)$ is the antiderivative of the distribution function $F(Q)$. Since the distribution function is monotonically increasing, the same holds for its antiderivative. This property of the functions helps to analyze the expressions in equation (21). It holds

$$
\begin{aligned}
\bar{F}(V_0 - q) - \bar{F}(0) &= \int_0^{V_0 - q} F(Q)\,\mathrm{d}Q \geq \int_0^{V_0 - q} F(0)\,\mathrm{d}Q \\
&= F(0)(V_0 - q),
\end{aligned} \tag{22}
$$

because the function $F(Q)$ increases in Q whereas $F(0)$ is a constant. Therefore the difference between the profits in (21) is always equal or smaller than zero and complete information always preferred.[33]

This result can also be shown graphically (Figure 11).

Figure 11: Typical curve progression of the cumulative distribution function



Source: Own presentation

[33] $E(\Pi^u) - E(\Pi^v) = 0$ would only hold in case $V_0 = q$.

The difference $\bar{F}(V_0 - q) - \bar{F}(0)$ is the area under the distribution function between the points $Q = 0$ and $Q = V_0 - q$. The expression $F(0)(V_0 - q)$ describes the area of a rectangle. It becomes obvious from Figure 11 that the area of the rectangle can never be larger than the area under the monotonically increasing distribution function.

For the second case, $V_0 - q < 0$, the lower limit under complete information is now $Q = 0$. It is directly visible that the expected profits under incomplete (20) and complete (12) information are identical. Hence, it holds for the difference

$$E(\Pi^u) - E(\Pi^v) = 0 \tag{23}$$

and the expected profit under complete information is never smaller than under incomplete information. ■

At first glance, it seems that the regime of incomplete information bears an advantage because the manufacturer can bring his product to the market for a wider range of outcome levels. But this advantage is overcompensated in case of $V_0 - q \geq 0$. The average product coming to market provides a lower benefit level under incomplete information than under complete information. This is correctly anticipated by the physicians. In case of $V_0 - q < 0$, the average benefit of a marketed product is the same under both regimes and the manufacturer becomes indifferent.

In total, a manufacturer would always prefer a regime of complete information over the regime of incomplete information, but also under the aspects of total welfare the regime of complete information is preferred. This will be demonstrated in the following.

The total expected welfare $E(W)$ is defined as the sum of the expected profit of the firm $E(\Pi)$ and the expected net benefit of the patient $E(V)$:

$$E(W) = E(\Pi) + E(V) \tag{24}$$

Under complete information the question about the net benefit of the patient is trivial. As the manufacturer sets his price p so that the patient is indifferent

between the new product and the comparator, the patient will always have a net benefit V_o. Under incomplete information it holds for the expected net benefit

$$E(V^u) = \int_{Q_a}^{0} \mathrm{V}_0 * \mathrm{f(Q)}\, dQ + \int_{0}^{Q_b} \big(Q + q - E(p|Q \geq 0\,)\big) * f(Q)\, \mathrm{d}Q \qquad (25)$$

Considering equation (13) and (19), the net benefit can be written as

$$E(V^u) = V_0 + \int_{0}^{Q_b} \left(Q - \frac{1}{1 - F(0)}\left[Q_b - \bar{F}(Q_b) + \bar{F}(0)\right]\right) * f(Q)\, \mathrm{d}Q \qquad (26)$$
$$= V_0$$

Therefore a risk neutral patient (respectively physician) is indifferent between both regimes. As expected profits are equal or higher under complete information, it follows $E(W^v) \geq E(W^u)$. Complete information is the preferred regime under the criterion of total welfare.

Given the motivation for the introduction of the AMNOG regulation, the results seem to contradict conventional political wisdom about the pharmaceutical market. It is often stated that pharmaceutical firms have no incentive for revealing the full information about the benefit of their products and would use the informational asymmetry to their advantage and overstate the benefits of their products.[34] But it seems rather that firms are not able to move into the regime of complete information credibly when they would like to. This aspect shall be further discussed later on.

The analysis above indicates that the subjective benefit q seems to be a critical parameter. It was shown that the manufacturer is indifferent between the regimes of complete and incomplete information when q becomes larger than V_0. But q was held the same in both regimes. In the next section this will be altered.

[34] See Schott *et al.* (2010)

VI.4.4 Introduction of the Early Benefit Evaluation of the G-BA

It has been shown above that the pharmaceutical firms have an incentive to reveal the benefit of their drugs, but they may not be able to do so. Under such circumstances the G-BA, as a public institution, can play the role of an objective source to reveal the medical evidence of a drug and create a regime of complete information. Based on the early benefit evaluation of the G-BA, the *GKV-Spitzenverband* and the manufacturer will decide about the price (see also section VI.1). In contrast to physicians and patients, the G-BA will only consider the measurable evidence based medical benefit Q and not the subjective benefit q. Consequently the price function for the *GKV-Spitzenverband* is modeled as

$$p^{GBA} = \max\{0, p_0 + Q - Q_0\} = \max\{0, Q - V_0\} \tag{27}$$

This assumption tries to capture the framework agreement between *GKV-Spitzenverband* and the manufacturer associations. In principle, the agreed price shall be appropriate for the identified additional benefit of the drug and represent a balance between the interests of the insured community and the pharmaceutical company.[35] Furthermore the parties shall ensure that prescriptions fulfill the universal requirements of appropriateness, quality, and effectiveness.[36] But the *GKV-Spitzenverband* has a significantly stronger position. This is captured in the following by the assumption that the *GKV-Spitzenverband* considers only Q in the negotiation process.[37] Honoring the requirements of dynamic efficiency (see section VI.2), the early benefit evaluation shall reward improvements in innovation. Where the net benefits are equal ($V = V_0$), the maximum rewarding price satisfies the requirements of cost-effectiveness and economic efficiency

---

35 See Spitzenverband Bund der Krankenkassen (2012)

36 § 130b (1) SGB V (Social Code Book 5)

37 An alternative approach would be a Nash bargaining solution. See for example Bardey *et al.* (2010) for such a modeling in the context of reimbursement pricing for pharmaceuticals.

because the ZVT is by definition appropriate and efficient. This leads to equation (27).[38]

Obviously the price function in (27) is equivalent to (4) after setting $q = 0$. Consequently all profit expressions and other functions under the G-BA regime can be derived directly from section VI.4.1 by setting $q = 0$. In conclusion the following Proposition is arrived.

Proposition 1: When the subjective benefit is not considered in a regime of complete information, then the regime of incomplete information is preferred by pharmaceutical producers for all $q > \hat{q} = \frac{\bar{F}(V_0) - \bar{F}(0) - F(0)V_0}{1 - F(0)}$. Whereupon it holds $0 \leq \hat{q} \leq V_0$.

Proof: First note that the case distinction $V_0 - q \geq 0$ respectively $V_0 - q < 0$ that was made in the case of complete information is not necessary anymore because effectively $q = 0$ and it always holds $V_0 > 0$. Based on equation (21), the difference is between the expected profit under incomplete information (20) with subjective benefit larger or equal to zero and the expected profit under complete information (11) with a subjective benefit set equal to zero. The difference can be written as

$$\begin{aligned} & E(\Pi^u) - E(\Pi^v | p^{GBA}) \\ &= \big(Q_b - \bar{F}(Q_b) + \bar{F}(0)\big) - \big(1 - F(0)\big)(V_0 - q) - c - (Q_b - V_0 - c) \\ &\qquad + \big(\bar{F}(Q_b) - \bar{F}(V_0)\big) \\ &= q + F(0)(V_0 - q) - \big(\bar{F}(V_0) - \bar{F}(0)\big) \\ &= \big(1 - F(0)\big)q + F(0)V_0 - \big(\bar{F}(V_0) - \bar{F}(0)\big) \end{aligned} \tag{28}$$

The critical value $\hat{q}$ is derived from setting this difference equal to zero. As $1 - F(0)$ is positive, the difference in profits is positive, and incomplete information preferred for all $q > \hat{q}$.

---

[38] Of course under static efficiency, the *GKV-Spitzenverband* would set the price low enough that the manufacturer is indifferent between leaving and staying in the market under the condition that the benefit of the drug is high enough ($p^{GBA} = \min\{c, \max\{0, Q - V_0\}\}$).

It remains to be shown that $0 \leq \hat{q}$ and $\hat{q} \leq V_0$. The expression $\left(\bar{F}(V_0) - \bar{F}(0)\right) - F(0)V_0$ can also be written as $\int_0^{V_0} F(Q) - F(0)\,\mathrm{d}Q$. Since the distribution function is monotonically increasing (see section VI.4.3.), the expression is positive. Therefore, numerator and denominator in $\hat{q}$ are positive. It is now shown that

$$\hat{q} = \frac{\bar{F}(V_0) - \bar{F}(0) - F(0)V_0}{1 - F(0)} \leq V_0 \tag{29}$$

The expression can be converted to

$$\begin{aligned} \bar{F}(V_0) - \bar{F}(0) &\leq V_0 \\ \int_0^{V_0} \mathrm{F}(Q)\,\mathrm{d}Q &\leq \int_0^{V_0} 1\,\mathrm{d}Q \end{aligned} \tag{30}$$

Obviously, this is always true as $F(Q) \leq 1$. ■

The regime of complete information is always preferred by the firms compared to both the regimes of incomplete information and the G-BA regime (i.e. $\mathrm{E}(\Pi^v) \geqslant \max\{E(\Pi^u), E(\Pi^v|p^{GBA})\}$). But when complete information cannot be achieved, firms would prefer the G-BA regime to incomplete information, if $q \leq \hat{q}$, implying $E(\Pi^v) \succ E(\Pi^v|p^{GBA}) \succ E(\Pi^u)$. In contrast, they prefer incomplete information over the G-BA regime if $q > \hat{q}$. For the case $\hat{q} < q \leq \mathrm{V}_0$, it holds $E(\Pi^v) \succ E(\Pi^u) \succ E(\Pi^v|p^{GBA})$ and under $\mathrm{V}_0 < q$ it holds $E(\Pi^v) = E(\Pi^u) \succ E(\Pi^v|p^{GBA})$.

These results show that the advantage of complete information depends on anticipating all benefits. This indicates why pharmaceutical companies might be reluctant to reveal the full benefit of their products, because they fear it could lead to a regulation similar to the G-BA regime.

Now the regime shall be investigated under the criterion of total welfare. Although the G-BA is not willing to pay the subjective benefit q, the patient still profits from it. Therefore, the expected net benefit is

$$E(V^v|p^{GBA}) = \int_{Q_a}^{V_0} V_0 * f(Q)\,\mathrm{d}Q + \int_{V_0}^{Q_b} (V_0 + q) * f(Q)\,\mathrm{d}Q = V_0 + \big(1 - F(V_0)\big)q \tag{31}$$

By considering the difference in profits from equation (28) and the expected benefit under incomplete information (26), the difference in expected total welfare is

$$E(W^u) - E(W^v|p^{GBA}) = \big(F(V_0) - F(0)\big)V_0 - \big(\bar{F}(V_0) - \bar{F}(0)\big) \tag{32}$$

By consulting Figure 11, it becomes obvious that it is easy to construct an example where the introduction of the early benefit evaluation leads to an increase in total welfare but also an example where total welfare decreases. This can be explained as follows. Under incomplete information the new product comes to market with a probability of $\big(1 - F(0)\big)$, but under the G-BA regime, the probability is only $\big(1 - F(V_0)\big)$. Hence, with a change of regimes the loss in expected profits for the manufacturer is higher than the gain in expected net benefit for the patient.[39] This aspect will be further discussed in the next section regarding the incentives for innovation.

VI.5 Decision process between different investments

It was shown in the former section that the introduction of the early benefit evaluation is an ambiguous reform under welfare aspects. But the legislator does not only want to achieve evidence based prices, he also wants to increase the incentive for more substantial innovations. This might give further understanding for the expedience of the AMNOG reform.

It is distinguished in the following between step innovations (s) and leap innovations (l). In case of a step innovation ("me-too" innovation), the

[39] It is implied that the manufacturer can induce the full q under the AMNOG reform. This could be questioned. A lower q would reduce the welfare under full information. Even further, it could be questioned if q should be part of the welfare at all when it does not provide real benefit for the patients.

manufacturer uses existing information and experiences. But then significant innovations are often not possible anymore. The result will most likely be a product with a similar benefit to the existing ZVT in the market. When the manufacturer invests into a leap innovation, he has to develop a new active principle for the treatment of the disease. The research expenditures are therefore higher and there is a chance for significant improvement in therapy. But it is also not unlikely that the research project will fail, as a new research approach might not work out in the end.

VI.5.1 Differentiation between leap and step innovation in the model

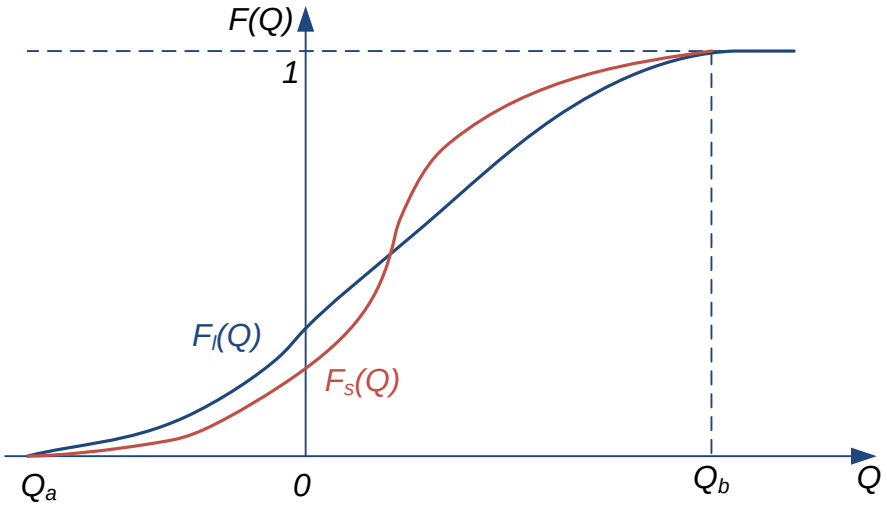
Transferred to the stochastic model discussed so far, this means that the investment into a leap innovation (l) shows a larger variance than a step innovation (s). Therefore the probability is higher under a step innovation process to develop a product that leads to a benefit of at least $Q = 0$. On the other side it also reduces the chance of a new product with a large additional benefit.

Thus it is assumed that

$$F_s(Q|Q < 0) \leq F_l(Q|Q < 0) \tag{33}$$

Figure 12 shows possible distribution functions based on this assumption.

Figure 12: Possible distribution functions for leap and step innovation



Source: Own presentation

The research costs also differ, as in case of a step innovation the manufacturer can rely on a greater pool of public knowledge.[40] From there it follows for the cost per patient

$$c_l > c_s > p_o \tag{34}$$

With these assumptions, leap and step innovations are sufficiently differentiated and it can be assumed that the subjective benefit is identical (35).

$$q_l = q_s = q \tag{35}$$

This assumption is reasonable as a leap innovation must not have an intrinsically higher subjective benefit. The latter can be independent from the medical benefit of a drug.[41] For example the new drug could be applied as a pill (high q) instead of an injection (low q) – both after a step or a leap innovative procedure. This plays only a minor role for the medical evidence but can have a significant impact on the compliance of the patients and the willingness of the physicians to prescribe the drug independently from the medical benefit of the drug. Furthermore, it was pointed out before that the variable q also expresses the

[40] See Bardey *et al.* (2010) and Croghan & Pittman (2004)

[41] See Höhle-Pasques *et al.* (2014)

ability of the company to induce benefits about its product. The skills of the marketing department should be independent from the specific innovation procedure.

As stated above, the introduction of the G-BA regime was politically motivated by the goal to affect companies' preferences, so that they would switch from step to leap innovation. In the terms of the model, this policy goal carries two implicit messages. Firstly, in cases where the expected profits under incomplete information are higher for an investment into a step innovation than into a leap innovation ($E(\Pi_s^u) > E(\Pi_l^u)$), they should turn around under the G-BA regime ($E(\Pi_s^v|p^{GBA}) < E(\Pi_l^v|p^{GBA})$). Secondly, the should not change their decision when a leap innovation was already preferred in the old regime. Before addressing this complex issue it will be investigated whether firms prefer leap or step under each of the information regimes.

VI.5.2 Complete information: Leap or Step?

Like in section VI.4 it must be distinguished between the case $V_0 - q \geq 0$ (including the special case under the G-BA regime) and $V_0 - q < 0$. For the first case, the difference between the expected profits can be derived from equation (11):

$$\begin{aligned} &E(\Pi_l^v) - E(\Pi_s^v) \\ &= (Q_b + q - V_0 - c_l) - \left(\bar{F}_l(Q_b) - \bar{F}_l(V_0 - q)\right) - (Q_b + q - V_0 - c_s) \\ &\qquad + \left(\bar{F}_s(Q_b) - \bar{F}_s(V_0 - q)\right) \\ &= (c_s - c_l) + \left(\bar{F}_s(Q_b) - \bar{F}_l(Q_b)\right) - \left(\bar{F}_s(V_0 - q) - \bar{F}_l(V_0 - q)\right) \end{aligned} \tag{36}$$

Corresponding to the assumptions in equation (34), the cost difference $(c_s - c_l)$ is negative. Regarding the other terms, the differences will depend on the specific distribution function. It will be shown below through an example that this difference can be positive or negative. This also extends to the G-BA regime which is equivalent to the case of $q = 0$

For the second case $V_0 - q < 0$ it can be derived from equation (12):

$$E(\Pi_l^v) - E(\Pi_s^v) = (c_s - c_l) - \big(F_s(0) - F_l(0)\big)(V_0 - q) + \big(\bar{F}_s(Q_b) - \bar{F}_l(Q_b)\big) - \big(\bar{F}_s(0) - \bar{F}_l(0)\big) \quad (37)$$

The final term $\big(\bar{F}_s(0) - \bar{F}_l(0)\big)$ is negative but it also holds that $\big(F_s(0) - F_l(0)\big)(V_0 - q) > 0$. Again, the difference can be positive or negative in the general model. This shall now be proven in a parameterized model which will be calibrated further in section VI.6.

The starting point for the parameterized model is a continuous uniform density function for Q. Reminding that the possible benefit levels are limited to $\Omega = [Q_a, Q_b]$, the density of the probability is

$$f(Q) = \begin{cases} \dfrac{1-\lambda}{Q_b - Q_a} & \text{for } Q \in [Q_a, Q_b] \\ 0 & \text{otherwise} \end{cases} \quad (38)$$

In addition it is assumed that there is a probability mass point at $Q = 0$ which has a probability $\lambda \in (0,1)$. It follows for the average $E(Q) = \frac{(1-\lambda)(Q_b+Q_a)}{2}$.

Leap innovation (l) and step innovation (s) are differentiated by the parameter λ. It holds

$$\lambda_l < \lambda_s \quad (39)$$

This way the condition of the general model in equation (33) is fulfilled.

In general terms, the profit function under complete information can be derived from equation (9) as

$$E(\Pi^v) = \lambda \max(0; q - V_0) + (1-\lambda)\left[\int_{\max(0;V_0-q)}^{Q_b} (Q + q - V_0) * \frac{1}{Q_b - Q_a} \mathrm{d}Q\right] - c \quad (40)$$

For the parameterized model however, the focus under complete information shall be on the investment decision under the G-BA regime. This is equivalent to $q = 0$ and only one case remains. Equation (40) can be written as

$$E(\Pi^v|p^{GBA}) = \frac{1-\lambda}{Q_b - Q_a}\left[\int_{V_0}^{Q_b}(Q - V_0)\,\mathrm{d}Q\right] - c = \frac{2c(Q_b - Q_a) + (Q_b - V_0)^2(\lambda - 1)}{-2(Q_b - Q_a)} \tag{41}$$

With this expected profit function, the differences between profits under leap and step innovation can be calculated. Inserting the expecting profit of the parameterized model into equation (36), leads to

$$\begin{aligned} &E(\Pi_l^v|p^{GBA}) - E(\Pi_s^v|p^{GBA}) \\ &= \frac{2c_l(Q_b - Q_a) + (Q_b - V_0)^2(\lambda_l - 1)}{-2(Q_b - Q_a)} \\ &\quad - \frac{2c_s(Q_b - Q_a) + (Q_b - V_0)^2(\lambda_s - 1)}{-2(Q_b - Q_a)} \\ &= \frac{2(c_l - c_s)(Q_b - Q_a) - (\lambda_s - \lambda_l)(Q_b - V_0)^2}{-2(Q_b - Q_a)} \end{aligned} \tag{42}$$

Recall that $(Q_b - Q_a) > 0, (c_l - c_s) > 0$ and $0 \leq \lambda_s - \lambda_l \leq 1$. When $(c_l - c_s)$ converges to zero it holds that the difference in expected profits is positive. On the other hand, there is always a sufficient cost difference $(c_l - c_s)$, that the difference in profits becomes negative. The influence of the benefit levels Q will be discussed later with help of the numerical values in section VI.6. However it shall already be noted here that an investment into a leap innovation is more probable with a wider range $(Q_b - Q_a)$.

Even though the legislator favors investments into leap innovations, it is questionable whether this is justified by economic consideration. Besides the profits, the net benefit for the patients must be investigated. Based on equation (31) and inserting the assumption of the parameterized model, the difference between consumer benefits under the G-BA regime is

$$\begin{aligned} &E(V_l^v|p^{GBA}) - E(V_s^v|p^{GBA}) \\ &= V_0 + \big(1 - F_l(V_0)\big)q - V_0 - \big(1 - F_s(V_0)\big)q \\ &= q\big(F_s(V_0) - F_l(V_0)\big) \\ &= q\left(\lambda_s + \int_{\mathrm{Q_a}}^{\mathrm{V_0}} \frac{(1-\lambda_s)}{Q_b - Q_a}\,\mathrm{d}Q - \lambda_l - \int_{\mathrm{Q_a}}^{\mathrm{V_0}} \frac{(1-\lambda_l)}{Q_b - Q_a}\,\mathrm{d}Q\right) \end{aligned} \tag{43}$$

$$= q(\lambda_s - \lambda_l)\frac{Q_b - V_0}{Q_b - Q_a} > 0$$

It can easily be seen that the expression is never smaller than zero because it holds $Q_b > V_0 = Q_0 - p_0$, as the benefit Q_0 of the comparator is part of the sample space Ω (refer to section VI.3). Even though the patients respectively physicians have a clear preference for leap innovation, it may not be the preferred investment decision under aspects of total welfare. As shown above large differences in development costs can overcompensate the medical preference.

VI.5.3 Incomplete Information: Leap or Step?

In case of incomplete information the difference between the profits of leap and step innovation can be derived from equation (20):

$$\begin{aligned} & E(\Pi_l^u) - E(\Pi_s^u) \\ &= \big(Q_b - \bar{\mathrm{F}}_l(Q_b) + \bar{\mathrm{F}}_l(0)\big) - \big(1 - F_l(0)\big)(V_0 - q) - c_l \\ &\qquad - \big(Q_b - \bar{F}_s(Q_b) + \bar{F}_s(0)\big) + \big(1 - F_s(0)\big)(V_0 - q) + c_s \\ &= (c_s - c_l) - \big(F_s(0) - F_l(0)\big)(V_0 - q) + \big(\bar{F}_s(Q_b) - \bar{F}_l(Q_b)\big) \\ &\qquad - \big(\bar{F}_s(0) - \bar{F}_l(0)\big) \end{aligned} \tag{44}$$

Note that physicians form equilibrium beliefs about the profit functions of the manufacturers. Given the specific parameters and anticipated information asymmetries, the manufacturer has a preference for leap or step innovation. The physicians can also consider these parameters through backward induction. Consequently, they know if the manufacturer chose a step or leap investment.

The investment decision shall be discussed in the parameterized model. At first the biased expected benefit of the new product must be calculated. The conditional probability function for the uniform distribution in the range $[0, Q_b]$ is

$$\begin{aligned} f(Q|Q \geq 0) &= \frac{f(Q)}{\int_0^{Q_b} f(Q)\mathrm{d}Q} \\ &= \frac{\frac{1-\lambda}{Q_b - Q_a}}{\lambda + (1-\lambda)\int_0^{Q_b} \frac{1}{Q_b - Q_a}\mathrm{d}Q} \quad \text{,for } Q \in [0, Q_b] \end{aligned} \tag{45}$$

and the conditional probability at the mass point $Q = 0$ is

$$\frac{\lambda}{\lambda + (1-\lambda)\int_0^{Q_b} \frac{1}{Q_b - Q_a} \mathrm{d}Q} \tag{46}$$

From there follows the expected benefit of the physicians for the new product:

$$\begin{aligned} E(Q|Q \geq 0) &= \frac{\lambda(Q_b - Q_a)}{(\lambda Q_a - Q_b)} * 0 + \frac{\lambda - 1}{(\lambda Q_a - Q_b)} \int_0^{Q_b} Q \, \mathrm{d}Q \\ &= \frac{(\lambda - 1) Q_b^2}{-2(Q_b - \lambda Q_a)} \end{aligned} \tag{47}$$

With this result, the expected profit under incomplete information can be calculated. Based on profit function in equation (20) the expected profit is

$$\begin{aligned} E(\Pi^u) = \; & \lambda(E(Q|Q \geq 0) + q - V_0) \\ & + \frac{(1-\lambda)}{Q_b - Q_a} \left[\int_0^{Q_b} (E(Q|Q \geq 0) + q - V_0) \, \mathrm{d}Q \right] - c \\ = \; & \frac{-2c(Q_b - Q_a) + (1-\lambda) {Q_b}^2 - 2(V_0 - q)(Q_b - \lambda Q_a)}{2(Q_b - Q_a)} \end{aligned} \tag{48}$$

From there follows the difference between expected profits for leap and step innovation:

$$\begin{aligned} & E(\Pi_l^u) - E(\Pi_s^u) \\ & = \frac{-2c_l(Q_b - Q_a) + (1-\lambda_l) Q_b^2 - 2(V_0 - q)(Q_b - \lambda_l Q_a)}{2(Q_b - Q_a)} \\ & \qquad - \frac{-2c_s(Q_b - Q_a) + (1-\lambda_s) Q_b^2 - 2(V_0 - q)(Q_b - \lambda_s Q_a)}{2(Q_b - Q_a)} \\ & = \frac{2(c_l - c_s)(Q_b - Q_a) - (\lambda_s - \lambda_l)\left(Q_b^2 - 2Q_a(V_0 - q)\right)}{-2(Q_b - Q_a)} \end{aligned} \tag{49}$$

Equation (49) differs from (42) only in the last term of the nominator. It can be positive or negative. This implies that step innovation is still preferred for a large cost difference. But a cost difference close to zero does not directly result in the investment into leap innovation. It only holds true when $V_0 - q > 0$. Whether this is a first indicator for an incentive to switch from step to leap innovation shall be discussed in the next section.

In regard to total welfare, the preference for leap or step innovation depends alone on the expected profits. It was shown in equation (26) that it holds $E(V^u) = V_0$. Hence, the patient is indifferent between the two investment decisions of the firm.

VI.5.4 Switching behavior

It is interesting to investigate whether the introduction of the early benefit evaluation leads to a switch in the investment decision. The legislator hopes that the disclosure of the medical benefit by the G-BA will give higher incentive to invest into leap innovations instead of step innovations. But it should be kept in mind that the opposite reaction is also possible.

For a switch from step to leap it must be investigated under which condition the following constellation is possible:

$$\text{Ante: } E(\Pi_s^u) > E(\Pi_l^u) \tag{50}$$

and

$$\text{Post: } E\left(\Pi_s^v | p_i^{GBA}\right) < E\left(\Pi_l^v | p_i^{GBA}\right) \tag{51}$$

In other words, under the regime of incomplete information the difference in equation (44), respectively (49) for the parameterized model, must be negative and under the G-BA regime the difference in equation (36), respectively (42), must be positive. Equation (50) and (51) can be written as

$$E(\Pi_l^v | p^{GBA}) - E(\Pi_s^v | p^{GBA}) > 0 > E(\Pi_l^u) - E(\Pi_s^u) \tag{52}$$

In section VI.5.2 and VI.5.3 it was shown that both differences can be smaller or larger than zero. Given the degrees of freedom in the model a general answer is not possible, but the parameterized model allows some first insights before the deeper investigation by a numerical approach in section VI.6.

Comparing equation (42) and (49) shows that the two inequalities in (52) can only be met if the following necessary condition is satisfied

$$\frac{(\lambda_s - \lambda_l)(Q_b - V_0)^2}{2(Q_b - Q_a)} > \frac{(\lambda_s - \lambda_l)\left(Q_b^2 - 2Q_a(V_0 - q)\right)}{2(Q_b - Q_a)} \tag{53}$$

Otherwise, the investment decision remains either the same under both regimes or the manufacturer switches from leap to step. Equation (53) can be simplified to:

$$\frac{V_0\left(V_0 - 2(Q_b - Q_a)\right)}{2Q_a} < q \tag{54}$$

By definition q is always positive and it can be shown that the same holds for the left side. The denominator is negative because $Q_a < 0$. The numerator is negative because V_0 is limited to $0 < V_0 \leq Q_b$ (see the appendix in section VI.9.1 for proof in detail). This indicates that q has to be large enough, so that a constellation is possible where the company chooses the step innovation under incomplete information and switches to leap innovation under the G-BA regime. It shall be noted here, that under $V_0 > q$, the condition in (54) can only hold when the mid-point of the density is larger than zero $\left(\frac{Q_b+Q_a}{2} > 0\right)$. It will be shown in section VI.6 that this constellation is rather unlikely.

The opposite scenario, a switch from leap to step innovation, is also possible. It must hold:

$$\text{Ante: } E(\Pi_s^u) < E(\Pi_l^u) \tag{55}$$

and

$$\text{Post: } E(\Pi_s^v | p^{GBA}) > E(\Pi_l^v | p^{GBA}) \tag{56}$$

As a consequence, the inequality signs must be turned around in (52) and (53). This way the necessary condition for a switch from leap to step innovation is derived.

Naturally, the aspect described in equation (50) and (51) can also be answered in regard to total welfare. In context of the parameterized model it was shown in equation (43) that patients prefer the leap innovation under complete information whereas they are indifferent under incomplete information (see equation (26)). In

consequence, it can already be stated that situations are possible where it is not profitable for the manufacturer to switch from step to leap innovation but it would increase total welfare if he did so. Adding the difference $E(V_l^v|p^{GBA}) - E(V_s^v|p^{GBA})$ of equation (43) to equation (53) leads to

$$\frac{(\lambda_s - \lambda_l)(Q_b - V_0)^2}{2(Q_b - Q_a)} + q(\lambda_s - \lambda_l)\frac{Q_b - V_0}{Q_b - Q_a} > \frac{(\lambda_s - \lambda_l)\left(Q_b^2 - 2Q_a(V_0 - q)\right)}{2(Q_b - Q_a)} \quad (57)$$

which can be simplified to

$$\frac{V_0\left(V_0 - 2(Q_b - Q_a)\right)}{2\left(V_0 - (Q_b - Q_a)\right)} < q \quad (58)$$

Equation (58) is a necessary condition for welfare to be increased by the G-BA system such that the latter induces a switch from step to leap innovation. Comparing equation (54) and (58) shows that $2\left(V_0 - (Q_b - Q_a)\right) < 2Q_a$. This is in line with the intuition that there is a higher interest for an investment into leap innovations for the patient than for the manufacturer.

VI.6 Numerical approach to the model

VI.6.1 Determination of parameters

The theoretical model shows that results depend on parameters. The following section is an attempt to identify realistic constellations for the different parameters. The arguments rely mainly on information from the evaluation process of the G-BA and official price information. It should also be kept in mind however that for some parameters public information is missing and assumptions are necessary.

G-BA resolutions

There are data available from the published resolutions of the G-BA, since the early benefit evaluation came into effect in 2011. By January 2015 (cut-off date:

January 15th, 2015), 69 new molecular entities (NMEs) went through the whole process of the early benefit evaluation by the G-BA (78 resolutions were published) and the price negotiations with the *GKV-Spitzenverband* (or opt-out during the negotiations process). A sample of 27 resolutions (corresponding to 24 NMEs) is used in the following for the numerical approach. The other evaluations were excluded for the following reasons:

- In 45 dossiers at least one ZVT was either a patent drug (see section VI.3: it is assumed in the model that the ZVT is generic), or best supportive care (BSC), or a non-medical treatment. Costs were not reported or were not comparable in the two latter cases.
- In one case a parallel import company carried out the price negotiation instead of the original inventor. The parallel importer has a different cost structure than a patent company.
- In one case only one generic producer was in the market and it seemed unlikely that the price was equal to production costs.
- In two cases the assumptions made here would have led to an entry price lower than cost (hence treated as outliers).
- In two cases, the pharmaceutical companies were allowed to hand in a revised dossier. Only the second dossier was considered here.

Because of these exclusions, the empirical evaluation is limited to 24 observations (see Table 20 in appendix VI.9.2. for an overview).[42] A resolution issued by the G-BA contains information about the annual therapy cost per patient for the new drug and the appropriate comparator. It also reports the number of potential patients for the treatment. The resolution always gives an upper and lower limit for the number of potential patients. In some cases the same is done for the annual cost per patient. In both cases the average is used for calculations here. When more than one indication per active ingredient were evaluated, the average costs per active ingredient were weighted by the number of patients per indication.

[42] Three NME went separately through separate evaluations for different indications. They were treated in each case as one evaluation.

Classification as leap or step investment

Regarding the classification of innovations into leap and step it is important to distinguish between the investment decision of the firm and the actual output. As the process is stochastic a leap investment can lead to a step innovation as output. The ascertained benefit in the resolution of the G-BA states whether the output of the new drug is a step or leap innovation relative to its comparator. But this does not say anything about the investment decision of the firm in the model. Another source is needed to specify the investment decision of the manufacturer. In an annual report of Fricke,[43] new pharmaceuticals are evaluated under pharmacological-therapeutic aspects. The concept ranks NMEs into four main groups A to D. NMEs of group A have an innovative structure or a novel mechanism of action with therapeutic relevance.[44] Hence, drugs of category A can be seen as the outcome of an investment into a leap innovation, all others as investments into step innovations. Concerning the data sample, 13 of the 24 NMEs were valued as category A drugs by Fricke and they are defined here as the results of leap investments. The remaining eleven evaluations are categorized as step investments. It is interesting to note that only three of the leap innovation investments (category A drugs) led to a leap innovation output receiving one of the two highest categories ("significant" and "major") in at least one indication by the G-BA. In case of the step investments, the G-BA granted none of them a significant or major additional benefit.

Production cost c_0

The production costs of the ZVT (c_0) are taken directly from the price information in the G-BA resolutions. In the model it is assumed that $p_0 = c_0$. For most evaluations more than ten providers offered a product for the appropriate

[43] See Fricke (2010-2014)

[44] See Fricke & Schwabe (2013), p. 48

comparator therapy. Empirical studies indicate that with such a number of competitors a price close to average production cost seems reasonable.[45]

Thus, the values given in Table 19 (see page 207) can be derived using the (weighted) prices of the appropriate comparators in the 24 evaluations as a proxy for c_0 (and p_0).

Production cost c_l and c_s

Regarding the average production costs c_l and c_s of the new drugs, the cost of R&D are the major difference to the cost of the comparator. The manufacturer needs to refinance the R&D costs through sales.

A study by Mestre-Ferrándiz *et al.* (2013) estimates the development cost for a new entity at 1,506 million (2011 US$). Capital cost are included. Converted to Euros (0.7661 US$/euro) and with assumed growth rate of 1.3 % in Europe and the US,[46] the costs for developing a new drug are 1,185 million (2013 euro). It can be assumed that new drugs need to finance themselves through sales mainly in the major industrial countries (Canada, European Union, Japan and the United States). The German market has a share of 6.0 % of the revenues in these four markets.[47] Therefore it is assumed, that the German market has to refinance the same percentage of the development costs. After market approval the company has 10 years of document protection. This can be seen as the (local) monopoly phase in the life cycle of the product. Within this time span the company has to refinance its development cost. Given an interest rate of 11 %,[48] a manufacturer has to refinance costs of 4.3m euro per year for R&D in Germany. Divided by the number of potential patients plus the cost c_0 of the comparator in the respective evaluation, an estimate for the costs per patient is given. This is done separately for each of the 24 evaluations. Corresponding to the classification of the

45 See Reiffen & Ward (2005)

46 See efpia (2013), p. 9

47 See BPI (2013), p. 45

48 See Mestre-Ferrándiz *et al.* (2013), p. 75

evaluations in leap and step, the average cost over all leap respectively step innovations is calculated to derive the values for c_l and c_s in Table 19 (see page 207).

Price before (p^{ante}) and after (p^{GBA}) price negotiation

For deriving the values of the other parameters in the model, the prices of the drug before and after the early benefit are needed as auxiliary variables. The annual therapeutic cost per patient reported in the resolution of the G-BA can be seen as the price p^{ante} ("ante price"**)** of the new drug before price negotiations. For the price p^{GBA} ("G-BA price") after price negotiations some assumptions and calculations are needed. The price per package[49] before and after price negotiation was taken from a pharmacy information software (Lauer-Taxe®).[50] In four cases the manufacturer opted out from the price negotiations. It is assumed that the price p^{GBA} would have been equal to p_0 of the ZVT.

The G-BA resolution allows to derive the number of consumed packages per year. The price difference times the number of annual packages gives the annual discount per patient granted by the manufacturer. This discount was subtracted from p^{ante} to receive p^{GBA}.[51]

Subjective benefit q

Based on the price functions in equation (4) and (27), the following must hold for p^{ante} and p^{GBA}:

$$\begin{aligned} p^{ante} &= Q + q - V_0 \\ p^{GBA} &= Q - V_0 \end{aligned} \tag{59}$$

---

49 The G-BA resolution defines the relevant package size and strength

50 The discount based on the price negotiations are published in the pharmacy software since February 2013. Manufacturers are legally obliged to inform about these discounts.

51 Until March 31st 2014 the granted discount was reported in a separate field in the software, since then it is priced into the list price of the manufacturer. In consequence, the margins for wholesalers and pharmacists sink. The lower margins were considered as savings on the G-BA price.

It is obvious that the subject benefit can be written as $q = p^{ante} - p^{GBA}$. Since p^{ante} and p^{GBA} are directly calculated, this gives q in Table 19.

Objective benefit Q_0 of the ZVT

The G-BA resolutions give no information on the actual monetary benefit of a drug. The additional benefit compared to the comparator is expressed on an ordinal scale of six categories reaching from "less" to "major".[52] Hence, an assumption for a reasonable benefit level is required. Under complete information a manufacturer would set a price where it holds for the benefit of the patient $V = Q - p = 0$, when he is the single provider of a medical treatment. The price would represent the benefit of the drug. Therefore it is not farfetched to use the post price p^{GBA} of the new drug as a proxy for the benefit Q_0 of the comparator. It should be pointed out that this also implies the assumption that all new drugs in the dataset have a benefit at least as high as their comparators. According to the model, it does not need to be the case, but given that none of the manufactures agreed on a price lower than the comparator price, the approach seems reasonable, even though four companies also preferred to opt out instead.

Objective benefit Q of the new drug

As it must (or should) hold after negotiations, that $V = V_0$ (see equation (3)), the benefit of the new drug is $Q = 2p^{GBA} - p_0$ (see Table 20 in appendix VI.9.2. for an overview of all benefit levels for the 24 evaluations).

Upper limit Q_b of the sample space Ω

The highest observable benefit can be used as a proxy for the upper limit Q_b of the sample space Ω for the random variable Q. The price p^{GBA} of a new drug was chosen, where BSC was the comparator. Given that BSC is not an actual treatment, cost and benefit are zero. A new drug could therefore charge the whole benefit as a price.

Probabilities λ_s and λ_l at the mass point

[52] § 5 (7) AM-NutzenV (The Ordinance on the Benefit Assessment of Pharmaceuticals)

For deriving the probabilities λ_s and λ_l, it can be taken advantage of the fact that only products are observed that received at least a benefit of $Q = 0$. The average over 22 available benefit levels (new and comparator) therefore represent the biased expected benefit $E_s(Q|Q \geq 0)$ for a step innovation and the average over 26 benefit level the biased expected benefit $E_l(Q|Q \geq 0)$ for a leap innovation (see Table 19). Based on equation (47), the probabilities λ_s and λ_l for the peaks can be expressed as function of Q_a, denoted by $\lambda_s(Q_a)$ and $\lambda_l(Q_a)$.

Lower limit Q_a of the sample space Ω

The possible values of Q_a can be narrowed down by condition $F_s(Q|Q < 0) \leq F_l(Q|Q < 0)$ in equation (33). The average success rates in bringing a product to the market can differ depending on the specific indication, time frame and market selection. The literature names a range of 3 % to 34 %.[53] Taken this into account, it should hold in the parameterized model $0.66 < (F_s(Q|Q < 0) \leq F_l(Q|Q < 0) < 0.97$, or using (45)

$$0.66 < \left(1 - \lambda_s(Q_a)\right) \int_{Q_a}^{0} \frac{1}{Q_b - Q_a} \mathrm{d}Q < (1 - \lambda_l(Q_a)) \int_{Q_a}^{0} \frac{1}{Q_b - Q_a} \mathrm{d}Q < 0.97 \quad (60)$$

This narrows down the possible values for the lower limit to $-24.57 * 10^6 < Q_a < -2.01 * 10^6$. In the following the mid-point ($Q_a = -13.29 * 10^6$) of the interval is used. This also implies that mid-point of the density is always smaller than zero: $\frac{Q_b + Q_a}{2} = -6.56 * 10^6$. Furthermore, the probabilities λ_s and λ_l can be set as $\lambda_s(Q_a) = 4.11$ % and $\lambda_l(Q_a) = 5.97$ % (see Table 19).

Calibration overview

The NME data used to derive the parameters are listed in Table 20 of the appendix (section VI.9.2). The calculated parameters themselves are reported in Table 19.

[53] See DiMasi *et al.* (2010) and Adams & Brantner (2006)

Table 19: Assumed Values for variables in the model

Variable	Value (euro)	Calculation
p_0	1,376	unweighted average over 24 active ingredients
Q_0	13,276	unweighted average over 24 active ingredients
q	4,692	unweighted average over 24 active ingredients
c_0	1,376	unweighted average over 24 active ingredients
c_l	2,039	unweighted average over 13 leap innovations
c_s	1,656	unweighted average over 11 step innovations
$E_l(Q \mid Q \geq 0)$	21,912	unweighted average over 13 leap innovations (including ZVT)
$E_s(Q \mid Q \geq 0)$	16,054	unweighted average over 11 step innovations (including ZVT)
Q_a	$-13.29*10^6$	Derived from equation (33) (see also appendix VI.9.2)
Q_b	182,495	Price p^{GBA} of Tafamidis
λ_l; λ_s	4.11 %, 5.97 %	Derived from equation (47) (see also appendix VI.9.2)

Source: G-BA (2015), Fricke (2010, 2011, 2012, 2013, 2014), LauerTaxe ®, own calculations

Note: All values are rounded to full euros.

Limitations of the derived parameters

Admittedly, some assumptions have been made in order to derive the results reported in Table 19. For various reasons costs c_0 are probably overstated. As there is no public information about the production cost of pharmaceuticals, the pharmacy sales prices of the ZVT were used as a proxy. But the sale prices per package include margins for pharmacies and wholesalers as well as valued added taxes. Furthermore, many generic drugs are under the reference price scheme. The G-BA calculates with the reference price, reduced by legal discounts, and not the actual, mostly lower, sales prices of the manufacturers. Finally, the majority of generic drugs is sold under individual discount contracts between manufacturers

and sickness funds.[54] These confidential discounts are also not considered by the G-BA. Overall, the actual marginal costs are probably lower than stated here.

Regarding the benefit levels and the prices of the manufacturer, it has been assumed that the negotiation partners are capable of quantifying the benefit in terms of willingness to pay and that the negotiation result is solely based on the benefit of the drug under evaluation.

VI.6.2 Interpretation of the model using the parameters of Table 19

From the results of Table 19 two aspects are emphasized. Firstly, the mid-point $\frac{Q_b+Q_a}{2}$ of the density is smaller than zero because the majority of research projects fail. Secondly, the net benefit V_0 of the comparator is larger than the subjective benefit q. Taking these two aspects into account further propositions about the model can be made and it can be shown that the AMNOG reform might not have had the desired effects on innovation strategies.

In regard to the reform two questions are of interest. Firstly, whether the companies would appreciate the change in the information regime through the AMNOG reform independently from their investment decision. Secondly, whether the companies will change their investment decision with the change of the information regime.

Preferences of the firms regarding the information regime

It was shown in section VI.4.4 that in general the firms prefer the regime of complete information. But when q is not considered in the price determination, a regime of incomplete information with q might become more profitable. When the observed q is larger then the critical $\hat{q}$ (see Proposition 1, page 188), the company would not like to give up the subjective benefit and would prefer a regime of incomplete information. Applying the parameterized model to $\hat{q}$ leads to

[54] See Häussler & de Millas (2014), p. 38

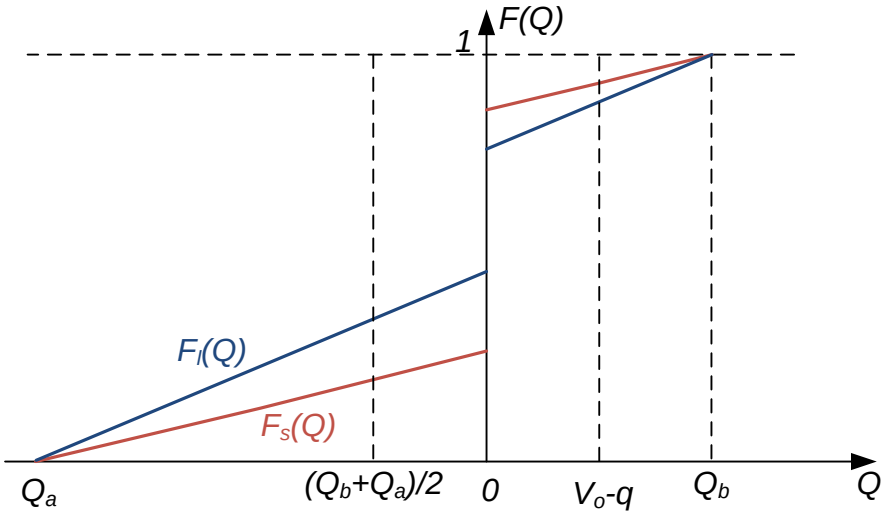
$$\hat{q} = \frac{(1-\lambda)\int_0^{V_0} \frac{Q-Q_a}{Q_b-Q_a}\mathrm{d}Q + \lambda V_0 - V_0 \int_{Q_a}^{0} \frac{1}{Q_b-Q_a}\mathrm{d}Q}{1-(1-\lambda)\int_{Q_a}^{0} \frac{1}{Q_b-Q_a}\mathrm{d}Q} \tag{61}$$

Note that $\hat{q}$ needs to be distinguished between $\hat{q}_s$ and $\hat{q}_l$ depending on the investment decision of the firm. The probability λ takes on the value $\lambda_s(Q_a)$ or $\lambda_l(Q_a)$. Consequently, it can be investigated whether the critical values $\hat{q}_s$ and $\hat{q}_l$ are larger or smaller than the derived subjective benefit $(q = 4{,}692)$ given in Table 19. In case of $\lambda_s(Q_a)$, it holds $\hat{q}_s = 9{,}875 > q$, implying that the companies would still prefer the regime of complete information even if they would loose the subjective benefit. The same holds in case of $\lambda_l(Q_a)$ as the critical value is $\hat{q}_l = 9{,}135$. In the dataset there is no step innovation where $q > \hat{q}_s$ and it only holds $q > \hat{q}_l$, for two of the leap innovations. It means that in general the subjective benefit q is small enough to be given up in favor of full reimbursement of the net benefit. It also indicates that companies would reveal the benefit of their products if they could. In conclusion, the companies would more likely appreciate the AMNOG reform.

Choice between investments for step and leap innovation

Now turning to the issue whether the change in regimes from incomplete information to complete information under the G-BA influences the investment decision. For the analysis, the focus can be on the distribution function as the difference in cost is a constant negative factor. In consequence, it has no influence on the switch of the investment decision (refer to equation (53)). Figure 13 shows the possible forms of the distribution functions for step and leap innovations in case of uniform distribution with a peak at $Q = 0$.

Figure 13: Possible curves of uniform distribution functions with peak at $Q = 0$ for leap and step innovation



Source: Own presentation

As seen on the figure, there is a jump in the distribution function at the peak and the original conditions $\lambda_s > \lambda_l$ and $F_s(Q|Q < 0) \leq F_l(Q|Q < 0)$ are interlinked. Equation (44) indicating the difference between the profits of leap and step innovation under incomplete information can be written as

$$\begin{aligned} E(\Pi_l^u) - E(\Pi_s^u) \\ &= (c_s - c_l) - \big(F_s(0) - F_l(0)\big)(V_0 - q) \\ &+ \big(\bar{F}_s(Q_b) - \bar{F}_s(0)\big) - \big(\bar{F}_l(Q_b) - \bar{F}_l(0)\big) \end{aligned} \tag{62}$$

It can be seen from Figure 13 that $\int_0^{Q_b} F_s(Q)\,dQ$ must be larger than $\int_0^{Q_b} F_l(Q)\,dQ$. The larger the difference between the areas the more the manufacturer will prefer an investment into a leap innovation. The difference between $F_s(0) - F_l(0)$ is always negative, which means that $\Big(-\big(F_s(0) - F_l(0)\big)(V_0 - q)\Big)$ is positive and makes a leap innovation more likely (the final decision depends from the difference in cost). Inserting the parameters of Table 19 leads to $E(\Pi_l^u) - E(\Pi_s^u) = -228.13$. Under these circumstances the firms would prefer the investment into step innovation. In order for an investment into a leap innovation to become profitable, the cost of the leap innovation must be

ceteris paribus lower, that is namely $c_l < 1{,}811$, or the range of possible outcomes narrower, that is namely $Q_a > -5.48 * 10^6$.

When the regime switches now from incomplete to complete information under the G-BA the difference between profits is based on equation (36) and can be written as

$$E(\Pi_l^v|p^{GBA}) - E(\Pi_s^v|p^{GBA}) = (c_s - c_l) + \left(\bar{F}_s(Q_b) - \bar{F}_s(V_0)\right) - \left(\bar{\mathrm{F}}_l(Q_b) - \bar{\mathrm{F}}_l(V_0)\right) \quad (63)$$

It can be seen easily that the positive factors in the equation are smaller in comparison to equation (62) and it is less likely that the firm will choose to invest into a leap innovation. Again, this can also be shown with the parameters. The difference in profits is negative: $E(\Pi_l^v) - E(\Pi_s^v) = -362.96$. This is a larger difference than under the regime of incomplete information. The difference in cost and the range of outcomes would need to be even smaller (namely $c_l < 1{,}676$ or $Q_a > -2.35 * 10^6$), in order for a leap investment to be preferred. In conclusion: the AMNOG reform has even increased the probability for a switch from leap to step investments.

It is obvious that the result is sensitive to the position of the peak and the form of the distribution function. When the peak shifts to the right it becomes more likely that the manufacturer will choose a step innovation under incomplete information and therefore a switch from step to leap under a new regime is more likely. In regard to the distribution function it is not farfetched to assume that the results would not change fundamentally. If the distribution were closer to a (left skewed) normal distribution, the intersection between the distribution functions would remain.

Welfare aspects

The patient is indifferent between the step and leap innovation under incomplete information, the difference in welfare is then equal to the difference of expected profits of the manufacturer. The patient would prefer the investment into a leap innovation under complete information of the G-BA regime. For the parameters in

Table 19 the sum of manufacturer's difference in profits (equation (42)) and patient's difference in benefit (equation (43)) is negative ($E(W_l^v) - E(W_s^v) = -361.86$). Hence, the investment into a step innovation is better for total welfare. Furthermore, the reform is an improvement because the manufacturer makes higher profits and the net benefit of the patients increases ($E(W_l^u) - E(W_s^v) = -659.12$); even though the intended outcome is not reached.

VI.7 Discussion

As stated in the introduction the legislator pursues three major goals with the introduction of the early benefit evaluation. Firstly, pharmaceutical prices should be based on the medical benefit of a drug. Secondly, they should act as an incentive for investments into "real" (i.e. leap) innovations. And thirdly, the evaluation should save costs compared to a system of free pricing.[55] In this paper, it was assumed that the parties are capable of finding a price that reflects the effectiveness of the drug and the focus was on the aspect of innovation. The saving aspect would be a (possible) consequence from the first two goals.

VI.7.1 Consequences from the change of regimes

The change in available information was identified as the major difference between the regimes before and after the early benefit evaluation. Even though study results for drugs are published and discussed a high level of uncertainty remains often about their interpretation and it is claimed that pharmaceutical companies are able to present their products more positively than they actually are.[56] Therefore, pharmaceutical companies might prefer a regime of incomplete information because it gives them room to manipulate information. The model shows that this is not necessarily the case. For a risk neutral pharmaceutical company, the expected profit under complete information (high variance) is

[55] See Cassel (2012)

[56] See Schott *et al.* (2010)

actually stochastically dominant over the expected profits under incomplete information (low variance). The reason is that it is not assumed that under incomplete information the manufacturer could just state a certain level of benefit, but the physicians are aware of the uncertainty and take into account that the benefit could even be lower than the one of the comparator. This seems to be more realistic than the (under-toned) allegation that physicians follow a "new is always better" paradigm and believe unconsideredly every claim by the pharmaceutical industry.[57] As a result the gain in profits for lower benefit levels cannot compensate for the loss of profits for higher ones.

Obviously the situation changes when revealing all information means losing a factor like the subjective benefit in the profit function of the model. Then the regime of incomplete information becomes a profitable option.

With the public revelation of the benefit level of a drug the legislator also hopes that the early benefit evaluation will foster the development of the "right" innovations. This is addressed in the model by introducing two investment choices for the pharmaceutical company. The investments differ in the variance of the possible outcomes with a high variance for a leap investment and low variance for a step investment. This implies that there is a high chance to develop a leap innovation through a leap investment but also a high chance of failure. For the analysis of the model, a specific distribution function was specified in section VI.5.3 and it was investigated with calibrated values in section VI.6. These further specifications led to the conclusion that the reform did not lead to the appreciated outcome. In case of incomplete information the profit is independent from the actual output, but the physicians grant the leap strategy a higher expected benefit than the step strategy. Hence, for every benefit level $Q \geq 0$, the sales after a leap investment are always higher than after a step investment and so are profits if the difference in cost is small enough. The higher profits in case of market approval can outweigh the lower chance of bringing a product to the market. In case of complete information sales are the same for every benefit level and therefore

[57] See Bauer & Wortzel (1966) and Black & Tagg (2007)

profits are lower for a leap innovation. The leap innovation can now only become more profitable over the greater chance of high outcomes.

The political goals of the reform might not be achieved but economically it is still an improvement because, as shown, welfare increases. Pharmaco-economic evaluations in view of static and dynamic efficiency (see section VI.2) are another aspect. Under the light of static efficiency, the early benefit evaluation keeps the patient at least indifferent (remember they also receive the subjective benefit q not priced in the profit function) between the old and the new drug. Static efficiency is achieved in the model as all potential patients can consume the product. The model here does not allow for a distinct answer in regards to dynamic efficiency but it shows that a well conducted early benefit evaluation grants the reimbursement of the inherit net benefit of a new drug. Recall that in equation (3) it was defined $V = V_0$, which leads under the G-BA regime to $Q - p^{GBA} = Q_0 - p_0$ (see section VI.6.1). Jena and Philipson (2008) state, that this would be the dynamically efficient maximization of the relation between cost and benefit. But the model shows that dynamic efficiency does not necessarily lead to the politically favored investment decisions.

VI.7.2 Reactions to the new G-BA regime

Beyond the choice between the investments into leap and step innovation, how could manufacturers react to the new regime? The analysis of 24 early benefit evaluations shows the difficulty to achieve a real leap innovation. Most NMEs show an additional benefit but it is not significant relatively to the comparator. It should be taken into account that for the reason of simplification, the G-BA here is capable of revealing all information about the objective benefit of a drug at the point of evaluation. In reality this is often not the case and is seen as a major reason for the poor results.[58] The manufacturers are not able to demonstrate the benefit of their drugs because for many therapies the medical benefit can only be shown in the long run. The G-BA is aware of this limitation. It grants some

[58] See Höhle-Pasques *et al.* (2014)

evaluation results only temporarily and reevaluates the drugs after some time.[59] But the underestimation seems not to be considered sufficiently in the price negotiations. It is claimed that this might lead to delayed market entries for new products in Germany. Manufacturers might wait until they have sufficient information to satisfy the G-BA.[60] The delay might lead to a higher reimbursement price but it would also increase the cost per patient because of the smaller time window to recover research cost. At the moment Germany still seems to be a preferred market for early access.[61]

There is also still a chance that the reform does not diminish the number of investments. They might even increase. The critical value would be the net benefit V_0 of the appropriate comparator. In general it can be said, that a manufacturer would prefer an indication with a low V_0 (see equation (41)). Current developments in the strategic orientation of pharmaceutical firms support this assumption. Many companies intensify their research efforts in fields like oncology or immune diseases.[62] In such indications there is still a high level of unmet medical need and companies can use a strategy of so called stratified medicine where specific patient groups within an indication are (genetically) identified for whom standard therapy does not work.[63] For these patients the new drug might be a leap in therapy whereas it shows no improvement for others. The investment into orphan drugs follows the same idea. Diseases with a prevalence of less than 5 patients per 10,000 inhabitants are defined as orphan.[64] Even small achievements would provide a high benefit for such diseases. However, a smaller patient group would also imply higher costs per patient given that development

---

59 See Osterloh (2014)

60 See Levaggi *et al.* (2013) for a theoretical approach regarding timing for market entry and buildup of knowledge

61 See Höer *et al.* (2014), p. 415

62 See for example Korzilius & Zylka-Menhorn (2013) and Kempe (2013)

63 See for example Million (2006) and Smart & Martin (2006)

64 See Westermark (2007)

cost are relatively independent from the number of potential patients. Furthermore, it would reduce the competition between pharmaceutical firms because each has its local monopoly. Sickness funds and legislators therefore see this development as critical.[65] However, it is not always certain for the companies that the higher prices can compensate the smaller number of patients.[66]

Such reactions from the pharmaceutical industry also show the potential conflicts between the goals through the early benefit evaluation. Benefit based prices do not imply savings for the health system. Because of the price structure $c > c_0 = p_0$, the price p for the new product must be higher than the price of the comparator, otherwise the product would not be profitable. Even when the benefit evaluation would filter out some products, the remaining ones would be more expensive than the comparator. As a consequence, the early benefit evaluation can only soften the increase in costs for pharmaceuticals, it cannot stop it.

VI.7.3 Model restrictions

Even though the model is able to describe the basic economic mechanisms behind the early benefit evaluation, some assumptions have been made that need to be considered. Most prominently, a static and well predictable environment is assumed. The manufacturer knows the numbers of its potential patients in a single indication, all patients receive the new drug when it offers the higher net benefit V and there is one single generic comparator.

Also it is assumed that the benefit is the same for every patient. The analyzed data set in section VI.6.1 shows that the market situation is more complex in reality. Most drugs are used in more than one indication and in many cases the manufacturer faces other patent drugs as competitors. Even though the G-BA

---

65 See Olvey & Bootman (2012) and Putzeist *et al.* (2013)

66 Vernon *et al.* (2006) and Danzon & Towse (2002) discuss this aspect theoretically in the context of market stratification through genetic tests. Whereas Vernon *et al.* (2006) see no advantage, Danzon & Towse (2002) see possibilities through the sales of the test itself and lower development costs.

chooses one comparator for every subgroup, there are other (more expensive) alternatives in the market. It is nearly impossible to serve the whole market. Of course, a pharmaceutical company can anticipate this and it will most likely calculate with a reasonable market instead of the theoretically treatable number of patients. In consequence, the market share could increase with the benefit of the drug. Then costs per patient would be lower for higher benefit levels and would make them more profitable. However, the G-BA defines the market for the new product based on the theoretical number of treatable patients for every approved indication and/or defined patient group. This could lead to disagreements about the cost per patient in the price negotiations. All these aspects make the whole evaluation process less predictable.

Furthermore, it should be kept in mind that the G-BA is not completely neutral. As mentioned in the introduction, the *GVK-Spitzenverband* is a member of the G-BA. The association acts as an agent for its sickness funds and the latter as agents of its members. Two goals follow from this. The *GKV-Spitzenverband* wants to ensure medical supply but also keep costs low. The treatment decision being based on the difference between benefit and price, the G-BA could use the scope of interpretation to define the benefit on the lower possible end. As long as it does not lead to an opt out by the manufacturer, this would be in favor of patients and insurants. This double role of the federal association as an "objective" agency and a "subjective" interest group is criticized by the pharmaceutical industry.[67]

In the end it is also a question whether the German early benefit evaluation can influence the investment decision at all. There are arguments for and against it. The 6 % share of the German market (see section VI.6.1) speaks against an influence. Pharmaceutical firms do not develop a product for just one national market but seek worldwide distribution. It seems unlikely that the German market itself is big enough to alter the investment decision of an international

[67] See Silies (2013), p. 134

manufacturer. Some experts only give that credit to the US market.[68] Germany however has an influence beyond its own market share through external reference pricing.[69] Germany is generally seen as a high price country. Pharmaceutical seek an early entry in Germany to define the upper price limit for other countries. A low additional benefit granted in Germany could jeopardize the market strategy in other countries.[70] Germany is a latecomer when it comes to the economic evaluation of pharmaceuticals. As discussed, other influential markets like France and the UK already implemented similar concepts.[71] The investment strategies may already have changed.

VI.8 Outlook and conclusion

With the introduction of the early benefit evaluation, the regulation of the German pharmaceutical outpatient market can be seen as completed. The market for patent drugs was the last refuge where companies could set their prices without legal restrictions or influences. Now they are actually the only market segment with fixed prices. Generics can charge a price over the reimbursement limit for the SHI system (the patient bears the difference) whereas the patent drug is bound to its negotiated price and the manufacturer can only lower it. A higher price is only possible after new evaluation and negotiation. With this policy Germany is now in line with most other European countries.

The AMNOG legislation was worked out under a liberal, business-friendly minister and is acknowledged by all political parties. Fundamental changes to the regime are unlikely in the future. The AMNOG is seen as a learning system and new governments might adjust details but the general approach will stay. Even though the paper here questions whether the AMNOG achieved all its intended

---

68 See Abbott & Vernon (2007) and Filson (2012)

69 See Tuomi *et al.* (2013)

70 See Danzon *et al.* (2005) and Kyle (2007)

71 See Kleijnen *et al.* (2011)

goals, under the aspects of welfare it is an improvement compared to the situation before the reform.

A surprising result in this paper is the advantage of the reform for the manufacturers. They profit from a regime of more complete information. The full reimbursement of the objective benefit for successful projects compensates the loss of minor research achievements and induced subjective benefits. The data indicate that the latter might not be as high as expected. Nevertheless, the pharmaceutical industry tried to prevent the AMNOG reform because in daily practice difficulties occur to objectify the benefit of a drug. For the treatment of chronic diseases it is nearly impossible to show the full benefit of a new drug in such an early stage of its life cycle. The requirements for validity can collide with ethical aspects in case of life threatening diseases. Such limitations lead to the underestimation of the real benefit of a drug. Furthermore the pharmaceutical industry is not convinced about the intentions of the joint self-government. Even though the G-BA and its members emphasize their intentions to reward innovations, thoughts about cost containment might predominate. This could lead to intentional undervaluation of new products. All these aspects reduce the positive effects of the early benefit evaluation for the pharmaceutical industry.

But even without such handicaps the model discussed here shows that the early benefit evaluation might not encourage the investment into potential “leap” innovations, i.e. a strategy with higher chances of a medical breakthrough but also of failed projects that never receive market approval. The pharmaceutical companies might rather choose to go with a safer investment strategy because the factors that might be irrelevant between different information regimes affect the investment decision within the same information regime.

Current market approvals are based on investment decisions taken about ten years ago or even longer. It is too early to say whether there is a significant observable change in the types of products entering the German market as a reaction to the AMNOG. Given the schemes of external reference pricing, it might be even more interesting to investigate what approved products do not enter the market. In that

context, the paper provides a theoretical outlook on how pharmaceutical firms might now change their investment behavior. Anecdotic evidence indicates that the firms do not necessarily seek leap innovations but try to identify (or create) therapeutic niches where even a small benefit level can be a significant step in therapy. The German benefit evaluation is only one among many in the world. It will be intellectually challenging to isolate the AMNOG as an influencing factor of this development.

VI.9 Appendix

VI.9.1 Proof that numerator is always negative

For the proof, it will be shown that the numerator is never positive. For a positive numerator it must hold that

$$\begin{aligned} V_0\big(V_0 - 2(Q_b - Q_a)\big) &> 0 \\ 2(Q_b - Q_a) &< V_0 \end{aligned} \tag{64}$$

On the other side V_0 is limited to

$$V_0 \leq Q_b \tag{65}$$

Hence the following must also be true

$$\begin{aligned} 2(Q_b - Q_a) &< Q_b \\ -2Q_a &< -Q_b \end{aligned} \tag{66}$$

As it holds that $Q_a < 0$ and $0 < Q_b$ equation (66) can never be true and therefore the numerator is never positive. ■

VI.9.2 Overview over considered active ingredients

Table 20: Considered active ingredients to derive values for the model

Active Ingredient	**Leap/Step-Investment (category by Fricke)**	**Leap/Step-Innovation (Granted additional benefit by the G-BA)**	**Potential Number of Patients**	**Price per patient (before negotiations): p^{ante}**	**Annual cost per patient (ZVT): p_0, c_0**	**cost per patient: c**	**Price per patient (after negotiations)/ Benefit of ZVT: p^{GBA}, Q_0**	**Drug benefit Q**
Cabazitaxel	Step (B/C)	Step (minor/not proven)	6,300	81,842	3,826	4,502	78,298	152,770
Regadenoson	Step (B)	Step (not proven)	41,000	86	22	126	70	118
Eribulin	Step (B/C)	Step (minor/less)	6,470	44,412	10,774	11,432	40,740	70,706
Collagenase clostridium histolyticum	Leap (A)	Step (minor)	35,000	1,960	577	699	577	577
Aliskiren, Amlodipin	Leap (A/C)	Step (not proven)	361,250	444	144	156	144	144

Active Ingredient	**Leap/Step-Investment (category by Fricke)**	**Leap/Step-Innovation (Granted additional benefit by the G-BA)**	**Potential Number of Patients**	**Price per patient (before negotiations): p^{ante}**	**Annual cost per patient (ZVT): p_0, c_0**	**cost per patient: c**	**Price per patient (after negotiations)/ Benefit of ZVT: p^{GBA}, Q_0**	**Drug benefit Q**
Apixaban	Step (C)	Step (minor / not proven/ minor)	1,399,500	1,090	183	186	951	1,719
Nabiximols	Leap (A)	Step (minor)	25,950	3,077	450	614	1,222	1,994
Belatacept	Leap (A)	Step (minor)	3,165	18,141	3,956	5,301	14,903	25,850
Belimumab	Leap (A)	Leap (major)	7,000	21,793	641	1,249	15,383	30,125
Bromfenac	Step (C)	Step (not proven)	925,000	21	11	16	13	15
Abirateron	Leap (A)	Leap (major / not proven)	28,200	99,353	4,578	4,729	75,576	146,574
Linagliptin	Step (C)	Step (not proven)	1,219,500	648	153	156	153	153
Perampanel	Leap (A/C)	Step (not proven)	88,700	3,260	490	538	490	490

Active Ingredient	**Leap/Step-Investment (category by Fricke)**	**Leap/Step-Innovation (Granted additional benefit by the G-BA)**	**Potential Number of Patients**	**Price per patient (before negotiations): p^{ante}**	**Annual cost per patient (ZVT): p_0, c_0**	**cost per patient: c**	**Price per patient (after negotiations)/ Benefit of ZVT: p^{GBA}, Q_0**	**Drug benefit Q**
Ruxolitinib	Leap (A)	Step (minor)	1,600	53,832	0	2,661	42,951	85,902
Metformin and Saxagliptin	Step (C)	Step (minor/ minor/ not proven)	801,450	749	312	317	670	1,028
Dapagliflozin	Leap (A/C)	Step (not proven)	896,100	905	257	265	596	936
Saxagliptin	Step (C)	Step (minor/ not proven/ not proven)	1,282,900	886	493	499	727	960
Sitagliptin	Leap (A/C)	Step (minor/ minor/ not proven)	1,804,800	827	374	378	721	1,067
Metformin and Sitagliptin	Leap (A/C)	Step (minor/ not proven/ not proven)	801,450	697	303	312	591	878
Ingenolmebutat	Leap (A/C)	Step (not proven)	2,182,500	130	74	78	67	59

Active Ingredient	**Leap/Step-Investment (category by Fricke)**	**Leap/Step-Innovation (Granted additional benefit by the G-BA)**	**Potential Number of Patients**	**Price per patient (before negotiations): p^{ante}**	**Annual cost per patient (ZVT): p_0, c_0**	**cost per patient: c**	**Price per patient (after negotiations)/ Benefit of ZVT: p^{GBA}, Q_0**	**Drug benefit Q**
Lixisenatid	Step (C)	Step (not proven)	903,000	1,448	283	291	540	797
Vildagliptin	Step (C)	Step (not proven)	1,805,400	865	374	378	652	930
Metformin and Vildagliptin	Step (C)	Step (not proven)	801,450	704	303	312	492	680
Vemurafenib	Leap (A)	Leap (major/ major)	1,400	94,069	4,443	9,529	42,110	79,776
Active Ingredient to define the upper limit Q_b								
Tafamidis	Leap (A/D)	Step (minor)	72	198,250	0	82,416	182,495	182,495

Source: G-BA(2015), Fricke (2010-2014) and LauerTaxe®. All numbers are rounded to full Euros.

VI.10 References

Abbott TA & Vernon JA (2007): The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions. *Managerial and Decision Economics* 28(4-5), 293-306. DOI: 10.1002/mde.1342.

Acemoglu D & Akcigit U (2006): State-Dependent Intellectual Property Rights Policy. December 2006. *NBER Working Paper Series No. 12775.* National Bureau of Economic Research. DOI: 10.3386/w12775. [Accessed: August 22nd 2014].

Adams CP & Brantner VV (2006): Estimating the cost of new drug development: is it really 802 million dollars? *Health Affairs* 25(2), 420-428. DOI: 10.1377/hlthaff.25.2.420.

Arvidsson G (1970): A note on optimal allocation of resources for R. & D. *The Swedish Journal of Economics* 72(3), 171-195. DOI: 10.2307/3438949.

Atun R & Gurol-Urganci I (2007): Uptake and diffusion of pharmaceutical innovations in health systems. *International Journal of Innovation Management* 11(2), 299-321. DOI: 10.1142/S1363919607001709.

Bardey D, Bommier A & Jullien B (2010): Retail price regulation and innovation: Reference pricing in the pharmaceutical industry. *Journal of Health Economics* 29(2), 303-316. DOI: 10.1016/j.jhealeco.2009.11.015.

Bauer RA & Wortzel LH (1966): Doctor's choice: The physician and his sources of information about drugs. *Journal of Marketing Research* 3(1), 40-47. DOI: 10.2307/3149433.

Black I & Tagg S (2007): A grounded theory of doctors' information search behaviour. Implications for information provision, pharmaceutical market entry and development. *Journal of Marketing Management* 23(3-4), 347-366. DOI: 10.1362/026725707x196413.

BPI [German Pharmaceutical Industry Association] (2013): Pharma-Data 2013. 43rd revised edition. Berlin. http://www.bpi.de/fileadmin/media/bpi/Downloads/Internet/Publikationen/Pharma-Daten/Pharmadaten_2013_EN.pdf [Accessed: August 22nd 2014].

Breyer F (2010): Zur Notwendigkeit indikationsübergreifender Nutzenmaße. *Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen* 104(3), 209-214. DOI: 10.1016/j.zefq.2010.03.004.

Busse R & Blümel M (2014): Germany: health system review. *Health Systems in Transition* 16(2), 1-296. ISSN: 1817-6127. http://www.euro.who.int/__data/assets/pdf_file/0008/255932/HiT-Germany.pdf [Accessed: August 22nd 2014].

Cassel D (2012): AMNOG: Deutschland an der Pharmawende. *pharmind - Pharmazeutische Industrie* 74(3), 366-374.

Chalkidou K, Tunis S, Lopert R, Rochaix L, Sawicki PT, Nasser M & Xerri B (2009): Comparative effectiveness research and evidence-based health policy:

experience from four countries. *Milbank Quarterly* 87(2), 339-367. DOI: 10.1111/j.1468-0009.2009.00560.x.

Chao RO & Kavadias S (2008): A theoretical framework for managing the new product development portfolio: when and how to use strategic buckets. *Management Science* 54(5), 907-921. DOI: 10.1287/mnsc.1070.0828.

Claxton K, Lacey LF & Walker SG (2000): Selecting treatments: a decision theoretic approach. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 163(2), 211-225. DOI: 10.1111/1467-985X.00166.

Croghan TW & Pittman PM (2004): The medicine cabinet: what's in it, why, and can we change the contents? *Health Affairs* 23(1), 23-33. DOI: 10.1377/hlthaff.23.1.23.

Danzon PM & Towse A (2002): The economics of gene therapy and of pharmacogenetics. *Value in Health* 5(1), 5-13. DOI: 10.1046/j.1524-4733.2002.51081.x.

Danzon PM, Wang YR & Wang L (2005): The impact of price regulation on the launch delay of new drugs--evidence from twenty-five major markets in the 1990s. *Health Economics* 14(3), 269-292. DOI: 10.1002/hec.931.

DiMasi JA, Feldman L, Seckler A & Wilson A (2010): Trends in risks associated with new drug development: success rates for investigational drugs. *Clinical Pharmacology and Therapeutics* 87(3), 272-277. DOI: 10.1038/clpt.2009.295.

Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ & Stoddart GL (2005): Methods for the Economic Evaluation of Health Care Programmes. 3. Edition. Oxford: Oxford University Press. ISBN: 0-19-852945-7.

efpia [European Federation of Pharmaceutical Industries and Associations] (2013): The Pharmaceutical Industry in Figures. Key Data 2013. Brussels. http://www.efpia.eu/uploads/Figures_Key_Data_2013.pdf [Accessed: August 23rd 2014].

Filson D (2012): A Markov-perfect equilibrium model of the impacts of price controls on the performance of the pharmaceutical industry. *The RAND Journal of Economics* 43(1), 110-138. DOI: 10.1111/j.1756-2171.2012.00159.x.

Fricke U (2010): Pharmakologische Bewertungen neuer Arzneimittel 2007-2009. *InVo - Informationen zu Verordnungen in der GKV* Februar 2010(2), 1-11. http://www.kvwl.de/arzt/verordnung/arzneimittel/info/invo/pharm_bewert_am_2007_2009_invo.pdf [Accessed: August 22nd 2014].

Fricke U (2011): Pharmakologische Bewertungen neuer Arzneimittel 2010. *InVo - Informationen zu Verordnungen in der GKV* Februar 2011(2), 1-3. http://www.kvwl.de/arzt/verordnung/arzneimittel/info/invo/pharm_bewert_am_2010_invo.pdf [Accessed: August 22nd 2014].

Fricke U (2012): Pharmakologische Bewertungen neuer Arzneimittel 2011. *InVo - Informationen zu Verordnungen in der GKV* August 2012(4), 1-5. http://www.kvwl.de/arzt/verordnung/arzneimittel/info/invo/pharm_bewert_am_2011_invo.pdf [Accessed: August 22nd 2014].

Fricke U (2013): Pharmakologische Bewertungen neuer Arzneimittel 2012. *InVo - Informationen zu Verordnungen in der GKV* April 2013(5), 1-6. http://www.kvwl.de/arzt/verordnung/arzneimittel/info/invo/pharm_bewert_am_2012_invo.pdf [Accessed: August 22nd 2014].

Fricke U (2014): Pharmakologische Bewertungen neuer Arzneimittel 2013. *InVo - Informationen zu Verordnungen in der GKV* Mai 2014(4), 1-7. http://www.kvwl.de/arzt/verordnung/arzneimittel/info/invo/pharm_bewert_am_2013_invo.pdf [Accessed: August 22nd 2014].

Fricke U & Schwabe U (2013): Neue Arzneimittel 2012. 2. In: Schwabe U & Paffrath D. Arzneiverordnungs-Report 2013. Springer Berlin Heidelberg, 47-120. ISBN: 978-3-642-37123-3.

Friederiszick H, Tosini N, de Véricourt F & Wakeman S (2009): An Econmic Assessment of the Relationship between Price Regulation and Incentives to Innovate in the Pharmaceutical Industry. [*White Paper*] *WP-109-03*. ESMT European School of Management and Technology. ISSN: 1866-4016.

G-BA [Gemeinsamer Bundesauschuss] (2014): The Federal Joint Committee. Berlin. http://www.english.g-ba.de/ [Accessed: October 9st 2014].

G-BA [Gemeinsamer Bundesauschuss] (2015): (Frühe) Nutzenbewertung nach §35a SGB V - Übersicht der Wirkstoffe. Berlin. https://www.g-ba.de/informationen/nutzenbewertung/ [Accessed: January 15th 2015].

Ganuza J-J, Llobet G & Domínguez B (2007): R&D in the Pharmaceutical Industry: A World of Small Innovations. Juli. *Economics Working Papers No. 0601*. Department of Economics and Business, Universitat Pompeu Fabra. ftp://www.cemfi.es/wp/06/0601.pdf [Accessed: August 21st 2014].

Ganuza J-J, Llobet G & Domínguez B (2009): R&D in the pharmaceutical industry: a world of small innovations. *Management Science* 55(4), 539-551. DOI: 10.1287/mnsc.1080.0959.

Giaccotto C, Santerre RE & Vernon JA (2005): Drug prices and research and development investment behavior in the pharmaceutical industry. *Journal of Law and Economics* 48(1), 195-214. DOI: 10.1086/426882.

Grinols EL & Henderson JW (2007): Replace pharmaceutical patents now. *PharmacoEconomics* 25(5), 355-363. DOI: 10.2165/00019053-200725050-00001.

Häussler B (2013): Seltene Krankheiten und die Arzneimittel zu ihrer Behandlung. In: Häussler B & Preuß K-J. Seltene Helden. Orphan Drugs in Deutschland. Düsseldorf: Fachverlag der Verlagsgruppe Handelsblatt, 1-22. ISBN: 978-3-942543-15-6.

Häussler B & de Millas C (2014): Arzneimittelausgaben der gesetzlichen Krankenversicherung im Jahr 2013 im Überblick. Kapitel 2. In: Häussler B, Höer A & Hempel E. Arzneimittel-Atlas 2014. Der Arzneimittelverbrauch in der GKV. Berlin, Heidelberg: Springer-Verlag, 3-48.

Höer A, Chen X & de Millas C (2014): AMNOG: Aktueller Stand der frühen Nutzenbewertung nach § 35 SGB V. Kapitel 5. In: Häussler B, Höer A & Hempel

E. Arzneimittel-Atlas 2014. Der Arzneimittelverbrauch in der GKV. Berlin, Heidelberg: Springer-Verlag, 383-418.

Höhle-Pasques S, Hankowitz J & Oberender P (2014): Drei Jahre frühe Nutzenbewertung nach §35a SGB V – kritische Würdigung und Lösungsvorschlag. *PharmacoEconomics German Research Articles* March 11th 2014, 1-12. DOI: 10.1007/s40275-014-0007-4.

Hurley J (2000): An overview of the normative economics of the health sector. Chapter 2. In: Culyer AJ & Newhouse JP. Handbook of Health Economics Volume 1, Chapter A. Elsevier, 55-118. ISBN: 978-0-444-50470-8.

IQWiG [Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen] (2013): Allgemeine Methoden: Version 4.1. Cologne. ISBN: 978-3-9815265-0-9. https://www.iqwig.de/download/IQWiG_Methoden_Version_4-1.pdf [Accessed: August 22nd 2014].

Jena AB & Philipson TJ (2008): Cost-effectiveness analysis and innovation. *Journal of Health Economics* 27(5), 1224-1236. DOI: 10.1016/j.jhealeco.2008.05.010.

Jena AB & Philipson TJ (2007): Cost-effectiveness as a price control. *Health Affairs* 26(3), 696-703. DOI: 10.1377/hlthaff.26.3.696.

Kanavos P, Nicod E, Espin J & van den Aardweg S (2010): Short- and Long-Term Effects of Value-Based Pricing vs. External Price Referencing. *EMiNet.* European Commission. http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/valuebased_pharmapricing_012010_en.pdf [Accessed: August 23rd 2014].

KBV [Kassenärztliche Bundesvereinigung] (2014): Verordnungssteuerung - Wirtschaftlichkeitsprüfung. Berlin. http://www.kbv.de/html/2949.php [Accessed: October 9th 2014].

Kempe L (2013): Medica 2013: Personalisierte Medizin: Modeerscheinung oder Megatrend? *Deutsches Ärzteblatt International* 110(46), 4. http://www.aerzteblatt.de/int/article.asp?id=149247 [Accessed: August 22nd 2014].

Kleijnen S, Goettsch W, d'Andon A, Vitre P, George E, Goulden S, Osińska B, Rdzany R, Zawada A & Thirstrup S (2011): EUnetHTA JA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals. Version 5B. July 2011. *Background Review.* EUnetHTA.

Korzilius H & Zylka-Menhorn V (2013): Arzneimittelforschung: Eine Industrie orientiert sich neu. *Deutsches Ärzteblatt International* 110(17), 820-824. http://www.aerzteblatt.de/int/article.asp?id=137615 [Accessed: August 22nd 2014].

Kyle MK (2007): Pharmaceutical price controls and entry strategies. *Review of Economics and Statistics* 89(1), 88-99. DOI: 10.1162/rest.89.1.88.

Levaggi R, Moretto M & Pertile P (2013): The Dynamics of Pharmaceutical Regulation and R&D Investments. [*Working Paper*] August 2013. *No. 13.* Department of Economics, University of Verona. DOI: 10.2139/ssrn.2306569.

Lichtenberg FR (2007): Importation and innovation. *Economics of Innovation and New Technology* 16(6), 403-417. DOI: 10.1080/10438590601002307.

Messori A, Cicchetti A & Patregani L (2010): Relating price determination to disease prevalence. *British Medical Journal* 341(7770), 417-418. DOI: 10.1136/bmj.c4615.

Mestre-Ferrándiz J, Sussex J & Towse A (2013): The R&D Cost of a New Medicine. London: Office of Health Economics. ISBN: 978-1-899040-19-3.

Million RP (2006): Impact of genetic diagnostics on drug development strategy. *Nature Reviews Drug Discovery* 5(6), 459-462. DOI: 10.1038/nrd2034.

Olvey EL & Bootman JL (2012): The 'fourth hurdle' of pharmacogenomics. *Pharmaceuticals Policy and Law* 14(1), 69-81. DOI: 10.3233/PPL-2011-0348.

Osterloh F (2014): Drei Jahre AMNOG: Erfolge und ein großer Makel. *Deutsches Ärzteblatt International* 111(18), 765. http://www.aerzteblatt.de/int/article.asp?id=159499 [Accessed: August 22nd 2014].

Paris V & Belloni A (2013): Value in Pharmaceutical Pricing. *OECD Health Working Papers No. 63.* OECD Publishing. DOI: 10.1787/5k43jc9v6knx-en.

Philipson TJ & Jena AB (2006): Surplus Appropriation from R&D and Health Care Technology Assessment Procedures. *NBER Working Paper Series No. 12016.* National Bureau of Economic Research. DOI: 10.3386/w12016.

Putzeist M, de Jong JP, Stolk P & Consultancy E (2013): Background Paper 8.2 Regulatory Structures to Support Pharmaceutical Innovation. *Priority Medicines for Europe and the World "A Public Health Approach to Innovation"*. http://www.who.int/medicines/areas/priority_medicines/BP8_2regulatory.pdf [Accessed: August 19th 2015].

Reiffen D & Ward MR (2005): Generic drug industry dynamics. *Review of Economics and Statistics* 87(1), 37-49. DOI: 10.1162/0034653053327694.

Saint-Paul G (2004): Are intellectual property rights unfair? *Labour Economics* 11(1), 129-144. DOI: 10.1016/S0927-5371(03)00057-5.

Schad M & John J (2012): Towards a social discount rate for the economic evaluation of health technologies in Germany: an exploratory analysis. *The European Journal of Health Economics* 13(2), 127-144. DOI: 10.1007/s10198-010-0292-9.

Schlette S & Hess R (2013): Early benefit assessment for pharmaceuticals in Germany: lessons for policymakers. *The Commonwealth Fund* 29(October), 1-10. http://www.commonwealthfund.org/Publications/Issue-Briefs/2013/Oct/Early-Benefit-Assessment-for-Pharmaceuticals-in-Germany.aspx [Accessed: August 22nd 2014].

Schott G, Pachl H, Limbach U, Gunder-Remy U, Ludwig W-D & Lieb K (2010): The financing of drug trials by pharmaceutical companies and its consequences. *Deutsches Ärzteblatt International* 107(16), 279-285. DOI: 10.3238/arztebl.2010.0279.

Silies H (2013): Erfahrungen mit den AMNOG-Preisverhandlungen aus Sicht der pharmazeutischen Industrie. In: Wille E. Wettbewerb im Arzneimittel- und Krankenhausbereich. *Allokation im Marktwirtschaftlichen System, Bd. 67*. Frankfurt am Main: PL Academic Research, 127-136. ISBN: 978-3-631-65007-3.

Smart A & Martin P (2006): The promise of pharmacogenetics: assessing the prospects for disease and patient stratification. *Studies in History and Philosophy of Science Chapter C: Studies in History and Philosophy of Biological and Biomedical Sciences* 37(3), 583-601. DOI: 10.1016/j.shpsc.2006.06.002.

Sood N, de Vries H, Gutierrez I, Lakdawalla DN & Goldman DP (2009): The effect of regulation on pharmaceutical revenues: experience in nineteen countries. *Health Affairs* 28(1), w125-w137. DOI: 10.1377/hlthaff.28.1.w125.

Spitzenverband Bund der Krankenkassen (2012): Rahmenvereinbarung nach §130b Abs. 9 SGB V. https://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/rahmenvertraege/pharmazeutische_unternehmer/Arzneimittel_Rahmenvereinbarung__130b_Abs9_SGB_V.pdf [Accessed: September 5th 2015].

Stonebraker JS (2002): How Bayer makes decisions to develop new drugs. *Interfaces* 32(6), 77-90. DOI: doi:10.1287/inte.32.6.77.6475.

Thürmann PA (2013): Die Frühbewertung des Zusatznutzens von Arzneimitteln aus ärztlicher Sicht. In: Wille E. Wettbewerb im Arzneimittel- und Krankenhausbereich. *Allokation im Marktwirtschaftlichen System, Bd. 67*. Frankfurt am Main: PL Academic Research, 107-120. ISBN: 978-3-631-65007-3.

Tuomi M, Rémuzat C, Vataire A-L & Urbinati D (2013): External Reference Pricing of Medicinal Products: Simulation-Based Considerations for Cross-Country Coordination. Final Report. December 2013. Brussels: European Commission. http://ec.europa.eu/health/healthcare/docs/erp_reimbursement_medicinal_products_en.pdf [Accessed: August 23rd 2014].

Vernon JA, Goldberg R & Golec J (2009): Economic evaluation and cost-effectiveness thresholds. *PharmacoEconomics* 27(10), 797-806. DOI: 10.2165/11313750-000000000-00000. [Accessed: August 22nd 2014].

Vernon JA, Hughen WK & Johnson SJ (2005): Mathematical modeling and pharmaceutical pricing: analyses used to inform in-licensing and developmental Go/No-Go decisions. *Health Care Management Science* 8(2), 167-179. DOI: 10.1007/s10729-005-0399-1.

Vernon JA, Johnson SJ, Hughen WK & Trujillo A (2006): Economic and developmental considerations for pharmacogenomic technology. *PharmacoEconomics* 24(4), 335-343. DOI: 10.2165/00019053-200624040-00004.

Westermark K (2007): The regulation of orphan medicines in the EU: Objectives reached and main challenges when facing the future. *Pharmaceuticals Policy and Law* 9(3), 327-342.

VII. Concluding remarks

The papers presented in this thesis shed light on different regulative instruments implemented in the German SHI drug market between 2004 and 2011. They can be seen in the broader goal of the regulator to set incentives for the development of innovative drugs through the pharmaceutical industry. Until 2011, the strategy was not to reward innovations but to penalize marketing of drugs that showed – in the opinion of the regulator - no improvement for the provision of care in Germany. The reintegration of patent drugs into reference groups in 2004 sets them on the price level of chemically and therapeutically equivalent generics. It also gives a signal to the physicians that active ingredients within the same reference price group are seen as interchangeable. The possibility of reduced co-payments for patients intensifies the price competition between generics and lowers the reference price for patent drugs even further. Giving quota for preferred active ingredients within therapeutic groups sets an additional incentive for physicians to prescribe cost-effective generics instead of patented alternatives. Rebate contracts do not directly enforce the competition between patented and generic drugs but they accelerate the phase of degeneration for the original drug after patent expiry and intensify the necessity to develop new products. The regulator changed his strategy with the introduction of the early benefit evaluation in 2011. Every new drug is evaluated and its "value" is determined. Hence, a higher valued drug will be rewarded with a higher price and pharmaceutical firms should consequently have an incentive to bring more innovative drugs to the market.

The various instruments were analyzed under the angle of different decision-making processes: first from the prescription decisions of physicians, then from the pricing and contracting decisions of pharmaceutical firms and sickness funds and last from the investment decisions of pharmaceutical firms regarding new

research programs. The results indicate that the regulations mostly achieved the desired effects.

The physician's perspective was used because he is a central stakeholder in the market. He decides what active ingredient will be consumed by the patient and because of his therapeutic freedom (within the ethic boundaries of medicine). The legislator cannot achieve its goals without the effective co-operation of the physicians. The introduction of lead compounds showed no significant effect on the prescription behavior of physicians but it must be kept in mind that this instrument misses a sharp implementation date which makes it more difficult to address it statistically. For the other instruments (reference price, exemption from co-payment and rebate contracts) a specific date can be specified. They all show a significant increase in the probability for physicians to change their prescription. Rebate contracts had the strongest effect. This is not surprising because they not only give the incentive for a specific active ingredient but also for a specific product. Furthermore, the probability for a change to a patent drug was lower than for most generic drugs. In conclusion, the changes went in the desired direction by the legislator.

The regulation instrument of rebate contracts showed the strongest effect. Because of that it was investigated further. Sickness funds and pharmaceutical companies are responsible for the implementation of such contracts. The thesis shows that sickness funds and manufacturers have an incentive to participate in rebate contracts. Sickness funds can increase the consumer rent of their insurants through lower prices and in part through higher consumption. The pharmaceutical companies gain a quasi-monopolistic market position and they have the possibility to perform price discrimination between different types of consumers respectively sickness-funds.

The preparation of the new regulation went alongside with the fear that the rebate contracts could lead to an oligopolistic market structure. The theoretical market analysis shows that this fear is legitimate. Large generic producers have a strategic advantage in the market. Firstly, some consumers show preferences for

specific brands and, secondly, large producers can offer a wide portfolio of different drugs. Hence, they can outperform smaller producers that provide only a limited selection of products. The legislator became aware of this risk for the contestability of generic markets. Portfolio contracts are not possible anymore and sickness funds tend to divide tenders in different lots even within the same active ingredient. The paper focused on the competition between two generic companies. The originator is already seen as irrelevant because the patent expired a long time ago. In a situation directly after patent expiry, rebate contracts could be a tool to expand the phase of saturation in the life-cycle or prevent immediate degeneration, because the originator gained a reputation in the market. But market data shows that research based pharmaceutical companies are reluctant to compete with generic companies.

In relation to the early benefit evaluation, the former regulative instruments differ in scope and information requirements. The reference price system covers only a specific part of drugs under patent protection. It can only pool pharmacological comparable active ingredients. The concept of lead compounds allows a broader perspective on therapeutically related active ingredients but it does not affect prices. Furthermore, it requires negotiations between sickness funds and regional associations for SHI physicians which are heavily influenced by political aspects. The early benefit evaluation is a much more comprehensive and objective concept, but it also requires more information. The reference price system focuses only on the observed prices and could be seen as driven by production costs. The willingness to pay as an expression of the medical benefit is not considered. The lead compound regulation considers the benefit of drugs based on experience in daily practice but there is no standardized procedure. In contrast, the early benefit evaluation uses international standards to define the benefit of a drug in relation to an established therapy. The final reimbursement price shall represent the willingness to pay of the German health system, and the pharmaceutical company receives (theoretically) the full consumer surplus. This way the legislator wants to create an incentive for more investments into projects that could result into a leap in medical care. But the theoretical analysis here shows that the new regime does

not lead to stronger incentives for riskier projects. The chance of higher reimbursement does not compensate the higher chance of failure. Nevertheless, there are also positive aspects. The pharmaceutical companies could invest more into fields with unmet medical need where the benefit of established therapies is low and an investment is more likely to lead to an innovation considered as a leap. Such indications also often have a small number of patients, which requires a higher price per patient given the high fixed cost. Based on positive evaluation results it will be easier to justify higher prices per patient.

The German pharmaceutical market is one of the last national markets with free pricing and unrestricted access for new pharmaceuticals. The reforms since 2004 targeted the aspect of free pricing but it is always in question if the current improvement in static efficiency harms the dynamic efficiency and therefore the access to potential new pharmaceuticals in the future. Normally, the market as a search process would address this problem, but as the thesis has shown, the provision of pharmaceuticals is not organized as a free market. Under the aspect of controlling the allocation process over prices, the possibilities seem fully exploited and further reforms will only alter details. Further actions would need to influence directly the research process of pharmaceutical firms.

Eidesstattliche Versicherung

(gemäß § 6 Abs. 1 Ziff. 4 der Promotionsordnung vom 30.11.2012)

1. Bei der eingereichten Dissertation zu dem Thema „Innovation, pricing and regulatory policies in the German pharmaceutical market“ handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt.

Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.

Ort und Datum Unterschrift

Eidesstattliche Versicherung
Belehrung

Die Universitäten in Baden-Württemberg verlangen eine Eidesstattliche Versicherung über die Eigenständigkeit der erbrachten wissenschaftlichen Leistungen, um sich glaubhaft zu versichern, dass der Promovend die wissenschaftlichen Leistungen eigenständig erbracht hat.

Weil der Gesetzgeber der Eidesstattlichen Versicherung eine besondere Bedeutung beimisst und sie erhebliche Folgen haben kann, hat der Gesetzgeber die Abgabe einer falschen eidesstattlichen Versicherung unter Strafe gestellt. Bei vorsätzlicher (also wissentlicher) Abgabe einer falschen Erklärung droht eine Freiheitsstrafe bis zu drei Jahren oder eine Geldstrafe.

Eine fahrlässige Abgabe (also Abgabe, obwohl Sie hätten erkennen müssen, dass die Erklärung nicht den Tatsachen entspricht) kann eine Freiheitsstrafe bis zu einem Jahr oder eine Geldstrafe nach sich ziehen.

Die entsprechenden Strafvorschriften sind in § 156 StGB (falsche Versicherung an Eides Statt) und in § 161 StGB (fahrlässiger Falscheid, fahrlässige falsche Versicherung an Eides Statt) wiedergegeben.

§ 156 StGB: Falsche Versicherung an Eides Statt

Wer vor einer zur Abnahme einer Versicherung an Eides Statt zuständigen Behörde eine solche Versicherung falsch abgibt oder unter Berufung auf eine solche Versicherung falsch aussagt, wird mit Freiheitsstrafe bis zu drei Jahren oder mit Geldstrafe bestraft.

§ 161 StGB: Fahrlässiger Falscheid, fahrlässige falsche Versicherung an Eides Statt

Abs. 1: Wenn eine der in den § 154 bis 156 bezeichneten Handlungen aus Fahrlässigkeit begangen worden ist, so tritt Freiheitsstrafe bis zu einem Jahr oder Geldstrafe ein.

Abs. 2: Straflosigkeit tritt ein, wenn der Täter die falsche Angabe rechtzeitig berichtigt. Die Vorschriften des § 158 Abs. 2 und 3 gelten entsprechend.

Ort und Datum Unterschrift