Transparency of Pharmaceutical companies

To what extent are net profits reinvested into the development of new drugs?

Erasmus University Rotterdam │ Master Thesis Health Economics

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SUMMARY

Introduction: Prescription drug prices continue to rise to exorbitant figures globally, contributing to the ongoing debate on why these prices are of this magnitude and keep on rising. Due to a lack of transparency in the pharmaceutical industry it is yet unclear how drug prices are being established and justified. Pharmaceutical companies claim the high prices are the result of long and intensive research and development (R&D) and high levels of risk accompanied with the development of a new drug. It is however questionable whether the economic data presented by pharmaceutical companies support these claims and therefore justify the exertion of a high drug price. The goal of this report can be summarized in the following research question: *To what extent do the economic data of pharmaceutical companies justify high budget impacts through the exertion of high prices?* In addition, this research report explores to what extent net profits are reinvested into the development of new drugs.

Methods: This research report combined qualitative and quantitative methods to enable a comprehensive evaluation of economic data presented in annual reports and financial databases. The pharmaceutical companies included in this study population consist of all companies that have a marketed drug in the Netherlands for which a financial arrangement was necessary for reimbursement to follow. A framework was constructed containing multiple variables which can be used to establish patterns and evaluate claims presented by the industry. An iterative process of annual reports review has led to the establishment of this framework. This framework consists of three main topics: reporting (1), variables (2), financial (3) and is used in answering the research questions regarding this study.

Results: The results have illustrated the differences in portfolio size, pipeline, product dependency and period of exclusivity in the sample which all contribute to different levels of risk and in the end influences the price determination of a drug. In addition, the average period of exclusivity in the sample is substantially higher than the theory and industry suggests. Some findings were consistent with the expectations. The results regarding the net profit/R&D ratio illustrate that in the sample, roughly an equal amount of money is spent on R&D as is being left as net profits in the company.

Conclusion: The lack of sufficient non-financial information in annual reports relating to retained profits, shareholder payouts and R&D expenses make it questionable whether there exists a certain policy regarding R&D reinvestments and the presence of a correlation between profits and R&D expenses. Significant differences exist in portfolio size, pipeline, product dependency and period of exclusivity which all contribute to different levels of risk companies bear. Even though there is homogeneity in the sample as the study population only concerns drugs with a high financial risk, substantial differences have been illustrated between the individual firms. Therefore, individual firms should not be able to hide behind the general known risks of this industry that may only apply for smaller, more innovative firms. It is desirable to elaborate on the findings in this study and further explore the variation between these pharmaceutical companies.

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1. INTRODUCTION

1.1 PROBLEM ANALYSIS

Prescription drug prices continue to rise to exorbitant figures globally, contributing to the ongoing debate on why these prices are of this magnitude and keep on rising (Nederlandse Zorgautoriteit (NZa), 2017).

The lack of transparency in the pharmaceutical industry makes it questionable how pharmaceutical companies arrive at their selling prices. Even though publicly listed pharmaceutical firms have a financial obligation to disclose financial statements (Securities Act of 1933), it is yet unclear how prices of new drugs are being established and justified.

Pharmaceutical companies claim the high prices are the result of long and intensive research and development (R&D) and high levels of risk accompanied with the development of a new drug. Moreover, they provide incentives for companies to invest and take necessary risks as a vast percentage of New Molecular Entities (NMEs) never make it to the market. (RVS, 2017) It is however questionable whether the economic data presented by pharmaceutical companies support these claims and therefore justify the exertion of a high drug price.

The continued rise in prices combined with the lack of transparency regarding the price setting raises the question whether current pricing is based on reasonable expectation of return on investment or whether it is based on what prices the market can bear. This would indicate that estimates are overstated by the industry and prices are justified to support risky R&D (Gavura, 2015). It is said to be possible that with the right incentives, R&D costs need not be an obstacle to the development of better medicines and prices could be much lower as well as the risk to the companies. (Light & Warburton, Demythologizing the high costs of pharmaceutical reseacrh, 2011)

Furthermore, once approved for sale, the pharmaceutical industry has a number of intellectual property rights to choose from to protect its drugs from competition, creating a monopolistic market. It is however unclear whether this is a form of overprotection of the pharmaceutical industry or whether these requirements are in fact necessary for the companies to reap back the high costs accompanied with the development of new medicines. Additionally, concerning the development of orphan drugs it is possible to obtain additional market exclusivity, further accentuating a monopolistic market. Therefore, high prices leading to high budget impacts increasing the costs of care make us question whether these prices are justified or are the result of exploitation by the pharmaceutical companies.

1.2 SOCIETAL RELEVANCE

New innovations being brought to the market can mean a significant improvement of the quality of life for many people. For others it can mean a valuable extension of life years left. New drugs are essential for good care and the development over time may bring better results but to what price is this considered to be acceptable? Medical treatments are priced out of the reach of the patients that need them, generating high budget impacts, presenting a system in which part of society may not be able to acquire the care they need.

One example in the US is the price of Sofosbuvir (Sovaldi®) which comes down to $84,000 for a 12-week treatment. Sovaldi®, product of Gilead Sciences, is used for treatment of the Hepatitis C virus (HCV) infection and the accompanied price has caused health insurers to refuse routine coverage of this drug. 64% of US HCV related spending in 2014 was accounted for by the use of Sovaldi® which totaled $12.3 billion. The budget impact of Sovaldi® is however too high to ensure availability to all U.S. patients with HCV infections (Boseley, 2015).

Moreover, also in the Netherlands routine coverage is not always granted. Nusinersen (Spinraza®), product of Biogen, is used for the treatment of spinal muscular atrophy (SMA) which is a rare inheritable muscle disease. At the moment, the costs per patient for the first year of treatment are on average €500.000 and for consecutive years €250.000 are to be expected which is far beyond the used reference value in the Netherlands (ZiN, 2018). This too means this drug is initially not reimbursed in the Netherlands and access to this drug may be denied to patients as the drug is priced out of their reach.

Pharmaceutical companies are able to remain solvable by maintaining large profit margins despite the relatively low productivity of R&D departments. The average profit margin in this industry exceeds 20% (Forbes, 2015) and raises the question whether this is acceptable and can merely be justified by extensive and risky R&D. Do all pharmaceutical companies bear the same amount of risk or are these merely statements made to exert a higher price? Furthermore, net profits should be reinvested into the development of new drugs with therapeutically high value but to what extent is this actually happening and is there a possibility that shareholders spend profits elsewhere?

Questions regarding abovementioned developments seem inevitable as prices keep on rising and care remains unaffordable.

1.3 OBJECTIVE & RESEARCH QUESTIONS

The aim of this research is to explore whether data presented by pharmaceutical companies support and justify the exertion of high prices leading to high budget impacts. Therefore, the transparency regarding available data of multiple firms will be analyzed and compared. Furthermore, will be explored whether the available data justify the exertion of high prices leading to high budget impacts. In order to provide an answer to the research questions, this report will attempt to construct a framework in which multiple collected variables are analyzed and compared within subjects and across industries. In this framework, the economic data will be further specified and categorized for analysis. The goal of this report can be summarized in the following main research question:

To what extent do the economic data of pharmaceutical companies justify high budget impacts through the exertion of high prices?

This study is conducted by three authors, myself included, in which we attempt to answer the same main research question by individually exploring different angles relating to this matter. This subsequently leads to three sub-questions regarding this study.

This thesis tries to examine whether net profits are reinvested into the development of new drugs. A better understanding of this could substantially add to the general acceptability of high profit margins in the pharmaceutical industry. Another possibility is the remittance of net profits to shareholders. The

objective of this thesis is therefore to determine how net profits are allocated. In order to address this matter, this research report will focus on the sub-question:

Q1: To what extent are net profits reinvested into the development of new drugs?

The following two sub-questions are not covered in this research report but do try to answer the same main research question.

Q2: How comprehensive, informative and socially acceptable are annual reports of pharmaceutical companies?

Q3: What is the means of transparency and to what extent do pharmaceutical companies pursue this?

Six chapters make up this thesis. In Chapter 2, I describe the main theoretical perspectives followed by the methodological approaches used in this research in Chapter 3. In Chapter 4, the most striking findings are presented. Subsequently, the most striking results are interpreted, discussed and compared with the literature in Chapter 5 upon which the research questions will be addressed. Finally, Chapter 6 concludes this thesis.

2. THEORETICAL FRAMEWORK

In this chapter, the theoretical background will be described in a literature review. The main concepts of the thesis questions will be addressed as well as contradictory results from previous studies.

2.1 THE PHARMACEUTICAL MARKET

Different types of prescription medicines

Before arguing the price setting of prescription medicines, a clarification is in order as to the distinct types of prescription medicines. A distinguished feature of the pharmaceutical market is the presence of intellectual property rights that provides a manufacturer with a temporary monopoly position. Therefore, a distinction can be made from drugs that are under patent protection with only one manufacturer and no competition and on the other hand generic drugs.

A first in class drug is an innovator drug that contains a new active ingredient acting on a newly defined patient population, whereas a generic drug contains the same active ingredient as the first in class drug and acts on the same population as well. Generic drugs enter the market when the patent protection of a first in class drug has expired. Generic drugs drive down the costs of healthcare spending by allowing for price competition (Godman et al, 2010). Moreover, generic drugs differ in the way that the development/registration process is much shorter and in general less expensive and are therefore able to exert lower prices. Due to the price competition after patent expiry, generic drugs stimulate meaningful innovation by innovators.

Considering me-too drugs, these drugs do not contain the same active ingredient as the first in class drug but do work on the same target population and are therefore referred to as 'me-too'.

Conventional drugs, mostly rather simple small-molecules, differ from biological drugs, complex protein-like substances. Biological drugs do follow the life cycle of conventional drugs but are more complex and are more often costlier to produce. This may allow for the acceptance of higher prices and for specific regulation of generic competition. In the case of biologicals, biosimilars compete with the innovator while following a specific set of regulations (Gronde, Uyl-de Groot, & Pieters, 2017). Because biosimilars are more challenging and expensive to generate, barriers to entry are higher than for small-molecule drugs (SMDs) (Morton & Kyle, 2012).

The severity of a condition also plays a role in societies' subjective determination of when a price is considered to be 'too high'.

Orphan drugs are targeted to patients suffering from rare, life threatening or chronically debilitating diseases and are subject to specific prevalence criteria. The prevalence of the disease in the EU must not be more than 5 in 10.000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development (EMA, 2018). Laws are in place to incentivize the development and marketing of orphan drugs, such as additional market exclusivity, which means that these drugs are subject to other market dynamics than conventional drugs (Gronde, Uyl-de Groot, & Pieters, 2017).

The pharmaceutical industry is a research-based industry where R&D is expected to account for roughly 30% of the total cost of developing, producing and marketing of new drugs (Danzon, 1997). In addition, new drugs do not emerge from R&D in a predictable way and the productivity of R&D is subject to change over time due to advances in technology and basic science. There are other industries that share several of these capital-intensive industry characteristics such as the software industry, however, they differ in the sense that the social welfare cost of a bad drug brought to market is considerably higher than that of bad software (Morton & Kyle, 2012).

There is an ongoing debate on whether R&D productivity has fallen over the years. When looking at the annual rates of R&D spending and the number of new molecular entities brought to market, one may observe a declining trend in R&D productivity (Mestre-Ferrandiz, Sussex, & Towse, 2012).

Several arguments relatable to this would be that 'low hanging fruits' have already been picked or more expensive and lengthy clinical trials due to more complex diseases targeted than years ago. The understanding of these costs is a key aspect to the global debate on reasonable drug prices and the magnitude of investments involved. It takes considerable time and risk to research, develop and gain approval for a new potential drug candidate and for that reason one should not focus solely on the static relationship between R&D spending and NMEs launched. Moreover, 9 out of 10 drug candidates do not make it to the market which contributes to a high amount of sunk costs (RVS, 2017).

This thesis additionally attends to the matter of profits reinvested in the development of new drugs. Therefore, it is important to understand the relationship, if any, between drug prices (eventually profits) and research & development. A study was conducted on drug prices and R&D investment behavior in the pharmaceutical industry by the university of Connecticut (Giaccotto, Santerre, & Vernon, 2005). The study population consisted of Major U.S. pharmaceutical companies and industry level data was used for the period 1952-2001. The study results indicate that pharmaceutical R&D spending increases with real drug prices. An estimated elasticity suggests that a 10% increase in the growth of real drug prices is associated with a nearly 6% increase in the growth of R&D intensity. Moreover, the results show that the capitalized value of pharmaceutical R&D spending would have been 30% lower if the federal government had limited drug price increases to the same growth as the general CPI during the period 1980-2001. Additionally, this drug price control would have resulted in approximately 330 fewer new drugs being brought to the market which means that roughly 38% of all new drugs would have been lost in the global economy if price controls were in order.

According to Donald Light and Rebecca Warburton (2011), pharmaceutical industries have a strong vested interest in maximizing figures for R&D. The industry's principle justification for its high prices on patented drugs has been the high cost of R&D. Subsequently, additional government protection is sought in the form of extended patent protection or data exclusivity without good cause that this would increase innovation. Previous research has provided reason that estimates of how risky and expensive R&D must be to develop medicines for global health problems ought to be lowered. Current incentives reward firms for developing new drugs with little therapeutically added value and then compete for market share at high prices. Rather development of clinically superior medicines with public funding should be rewarded so that prices could be much lower (Light & Warburton, Demythologizing the high costs of pharmaceutical reseacrh, 2011).

Small research-oriented firms

One clear distinction of this industry compared to several other industries is the degree of regulation which clearly is inevitable considering public health. However, the imperative of regulation makes it harder for smaller firms to register a new drug. The importance of these smaller companies should not be considered lightly as most often these smaller companies are critically important during the early phases of discovery and development. If the new molecular entity turns out to be a success it is likely that a larger pharmaceutical company will try to acquire the small company or purchase the license for the drug (Lincker et al, 2014).

Obviously, the acquisition of a smaller company requires great capital but at the same time implies less pressure is put on in-house research and development which can lead to the shifting of risk. Therefore, the link between acquisition and R&D will be explored within the scope of this thesis.

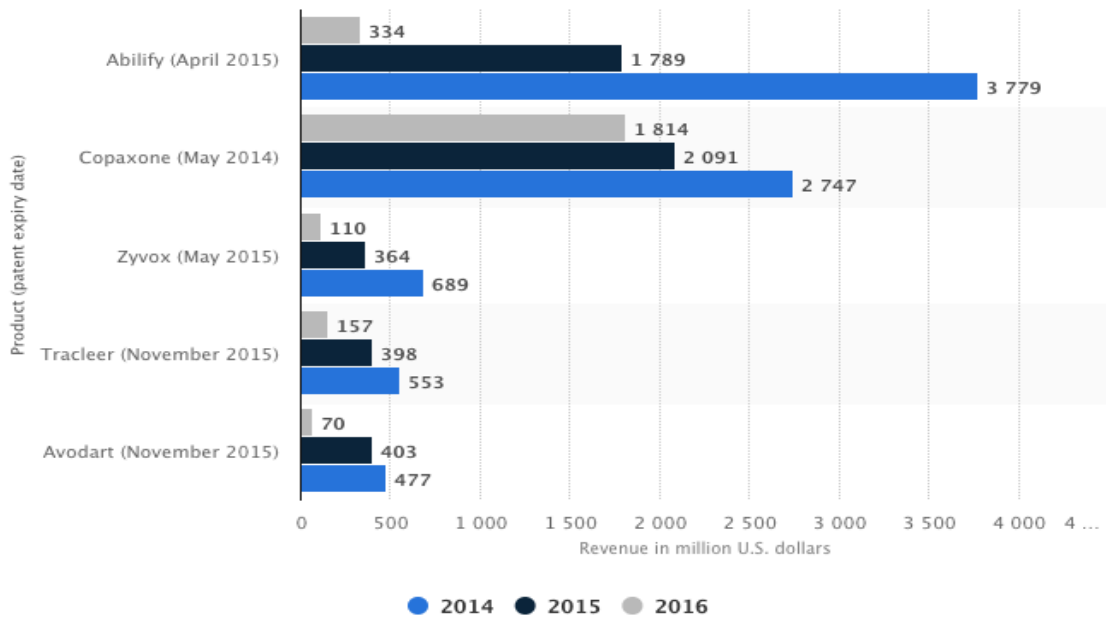## THE ECONOMIC ROLE OF PATENTS

Intellectual property protection leads to the award of a patent, which grants the holder a monopoly right to produce and market goods and services for the duration of that patent (Goldman & Lakdawalla, 2012).

With the absence of patents, generic drugs could enter freely and because of the competition, drug prices would be forced downwards to the marginal cost of production and distribution, ignoring the R&D expenses of the innovator firms. This marginal cost pricing would generate insufficient revenue to cover the R&D expenses of innovator firms. This competitive market form would not be in line with the sustained incentives for R&D.

The economic purpose of patents is therefore to prohibit entry of generic drugs for the duration of the patent, to provide the innovator firm with an opportunity to retrieve R&D expenses by setting the price above marginal cost. This assures incentives for future R&D. (Danzon & Towse, 2003)

From a utility maximizing perspective, every consumer with a marginal benefit higher than marginal cost concerning the specific drug should use the drug. In practice this does not happen due to the pricing above marginal cost, justified to regain R&D expenses and to sustain innovation. In general, a patent expires after 20 years from the initial date on which the application was filed. In cases when there has been filed for supplementary patent protection and this has been granted, this period can be extended to 25 years.

Figure 1. Product revenue effect of patent expiration

Source: (Statista)

Figure 1 Illustrates the effects of patent expiration on the product revenue for 5 different drugs.

The economic purpose of patents is therefore to prohibit entry of generic drugs for the duration of the patent, to provide the innovator firm with an opportunity to retrieve R&D expenses by setting the price above marginal cost. This assures incentives for future R&D. (Danzon & Towse, 2003)

Figure 2. New medicines timeline
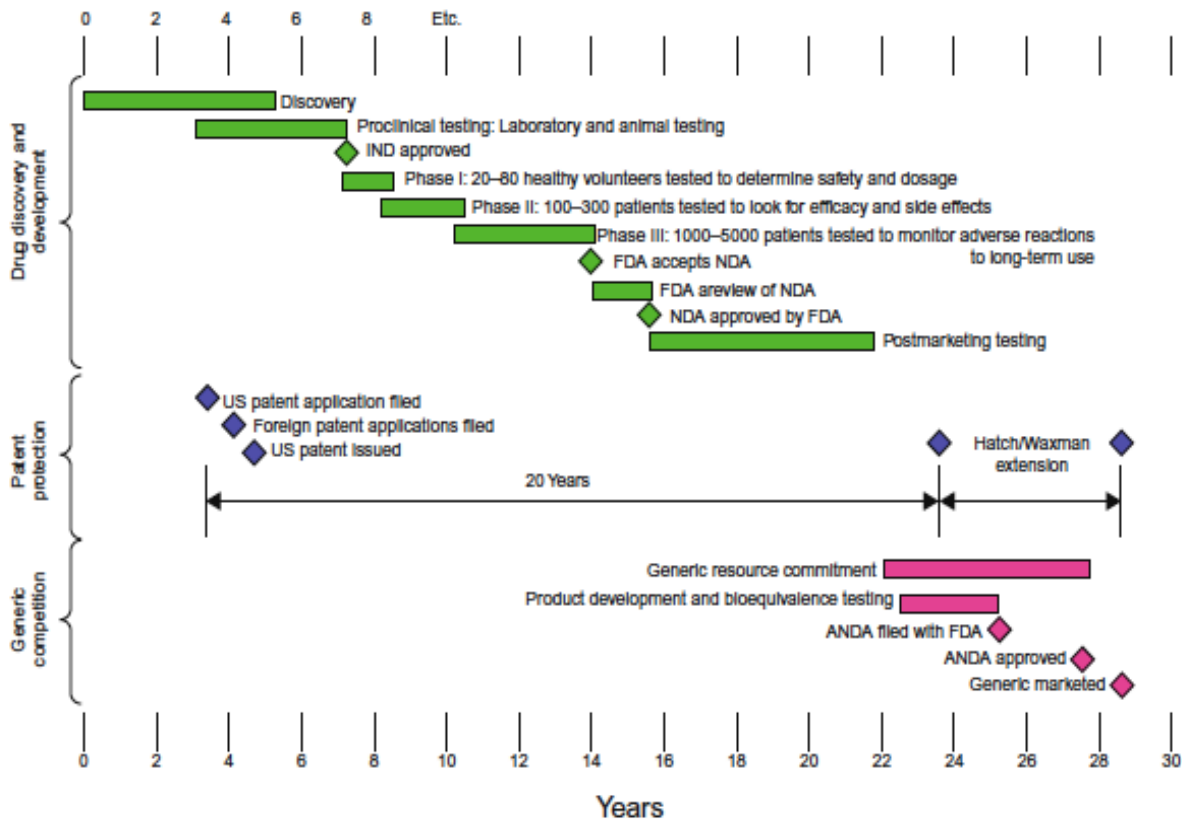
Source: (Goldman & Lakdawalla, 2012)

As figure 2 portrays, once a drug can be marketed and approval is granted, there is roughly 7/8 years left of patent protection. According to the European Federation of Pharmaceutical Industries and Association (EFPIA) drug screening and development accompanied with the administrative hurdle takes around 12-13 years (EFPIA, 2016). In the case of orphan drugs, the EMA (European Medicines Agency) may grant an additional 10 years of market exclusivity that starts after approval and may exceed the patent period. Moreover, because of the limited patent timelines, incentives arise to shorten the development phase of drugs or to commit to research and development in areas with less strict clinical trial requirements (Gronde, Uyl-de Groot, & Pieters, 2017). There is for example more research in drugs for late-stage cancer than early-stage cancer due to less strict and shorter trial phases.

Figure 3. General life cycle of a drug
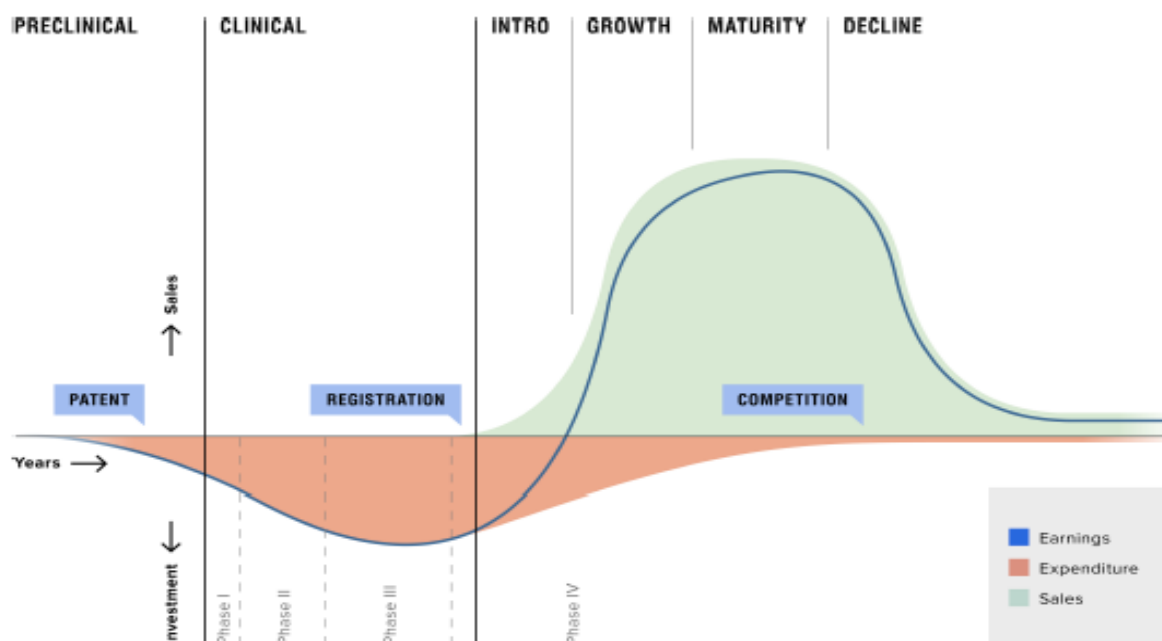
Source: (Gronde, Uyl-de Groot, & Pieters, 2017)

Over the years the development of drugs has evolved such as the complexity of molecules. In the early stages, most of the drugs developed used to be chemicals discovered by random screening, whereas now 'rational drug design' has evolved in which biological processes are used and have already revolutionized the treatment of many diseases. In the research phase, new molecular entities are discovered either by phenotypical screening or target-based pharmacology (RVS, 2017).

Once a drug candidate has been identified, preclinical testing follows in animal subjects. If results are promising, then an Investigational New Drug (IND) filing follows with regulatory authorities (Morton & Kyle, 2012). The drug candidate is then tested in clinical trials, the first phase involves a small number of healthy patients to establish safety and efficacy of the drug. Phase 2 entails a larger number of patients in order to establish quality & efficacy in addition to safety. Phase 3 trials are randomized control trials, often conducted in multiple locations and are often the costliest phase although dependent on the disease. In addition, clinical testing is accompanied by a high level of risk as the odds of having a drug approved can vary from approximately 24% to less than 10% for drugs used to treat cardiovascular or metabolic disorders (Miller, 2010). Therefore, a well-considered evaluation needs to be done when deciding what projects to choose that may add therapeutically high value and future profits. An even larger number of patients, if available, is used in phase 3 to establish efficacy and comparative effectiveness as in this last pre-registration phase a comparison is made with the current golden standard. Studies have estimated phase transition success rates and found that the probability of success from phase 3 to New Drug Administration filing is 58.1% (n= 1491) and in the case of hematology indications 75.0% (n=64) (Thomas, et al., 2016). Phase 4 trials are post registration with the aim to detect potential long term adverse effects. Studies are done in real life as opposed to randomized controlled trials. If successful, the compound will be registered with the regulatory authority, the European Medicines Agency in Europe, allowing the new drug to enter the market if approved. This is all part of the testing and approval trajectory in the life cycle of a drug.

Introduction & growth phase

In the first phase after registration it is critically important for the manufacturer of the drug that the product is used as quickly as possible. This has to do with the exclusivity period which is considered essential in maximizing profits. Therefore, there needs to be a high level of market penetration and one way of achieving a high level of market penetration is due to marketing efforts. In the US, products are directly advertised to pharmacists doctors and patients, however, directly advertising to patients is illegal in most other countries which may have a considerable effect on turnover in the early stages. Directly marketing to pharmacists and doctors is allowed in Europe if it is medically substantiated and is considered important in the early phases of developing a new drug (Gronde, Uyl-de Groot, & Pieters, 2017). In addition, marketing expenses are said to be greater than R&D expenses as less money is spent on R&D nowadays (Moors, Cohen, & Schellekens, 2014). Therefore, selling general and administrative costs, in which marketing is often a big part, will be compared to the R&D costs in this thesis.

Above all, drugs are experience goods and usage depend on satisfactory experience (Ellery & Hansen, 2012). New drugs need to keep on providing therapeutically added value compared to already available drugs. Therefore, the growth curve may be steeper for a drug used to treat an untreatable or uncontrolled disease and less steep for a me-too drug.

Maturity Phase

In the maturity phase, companies try to register for new indications as this would result in an additional period of exclusivity and perhaps also target a larger patient population. The goal of this is to increase their sales volume because most often after patent expiration, a sudden start of the decline phase begins which means a drop in sales. Most drugs therefore lack a true maturity phase (Ellery & Hansen, 2012).

Figure 4. Desired growth curve vs. usual growth curve of most drugs
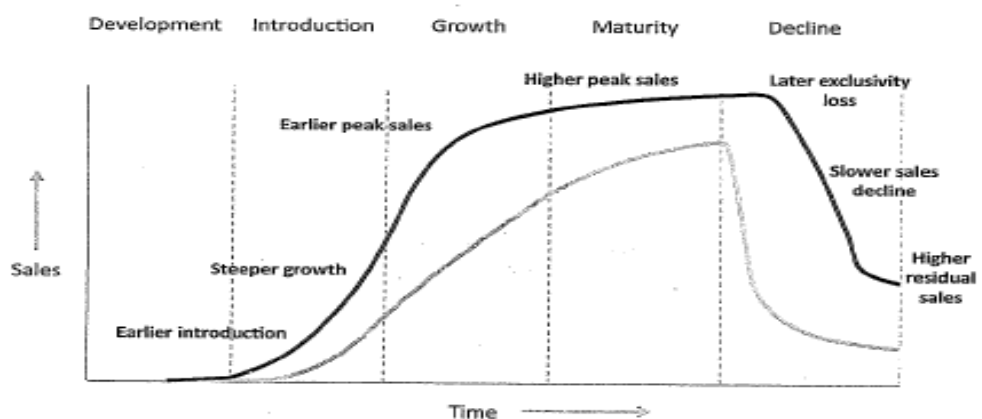

Source: (Ellery & Hansen, 2012)

Decline phase

At patent expiry, generic drugs enter the market which may and most often will lead to generic substitution. Generic substitution puts a limit on the length of a life cycle of patented innovator drugs since they are replaced by generics as soon as their patent expires (Gronde, Uyl-de Groot, & Pieters, 2017). This most often reduces the time in which innovator drugs can generate income. One viable strategy for the brand company is to focus on 'laggards' who are suspicious of generic drugs and are loyal to branded drugs because of satisfactory experiences. (Ellery & Hansen, 2012) This substitution effect is however much smaller for biological drugs as it is much more challenging to copy these drugs. Moreover, the drop in price in cases of biosimilar substitution after patent expiration is often merely 20-30% whereas the price drop for smaller chemical molecules can fall by more than 70% (Bagel, 2014).

2.3 PRICING

Over the years, the decline in the number of NMEs launched combined with the downward pressure on prices has increased the importance of realizing adequate returns from those NMEs launched. A pharmaceutical company needs to estimate the value of the drug to its customers, but also the willingness to pay and affordability (Gregson, Sparrowhawk, Mauskopf, & Paul, 2005). In addition, the company needs to determine a price threshold above which the return on investment will be sufficient for its investors.

Value-based pricing in the context of the pharmaceutical industry comes down to assessing the value of a drug compared to alternatives present and setting a price relative to that value.

Figure 5. Value based pricing
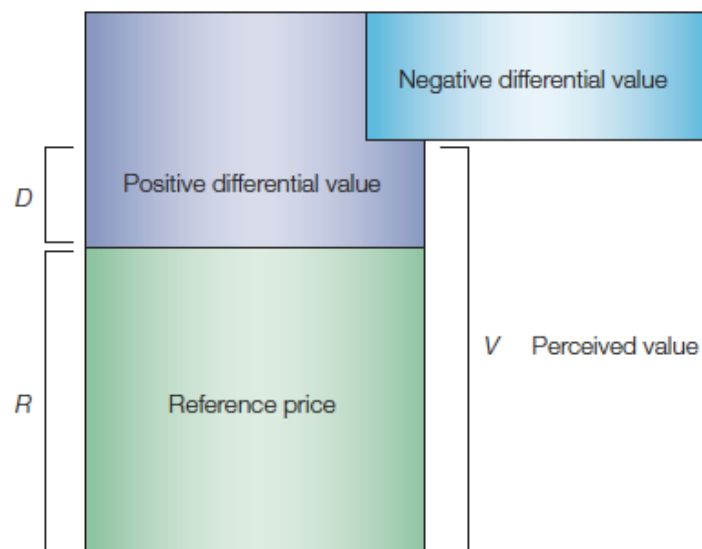
Source: (Gregson, Sparrowhawk, Mauskopf, & Paul, 2005)

In this setting, the perceived value of a drug is equal to the reference price, which is the price of the best alternative reference product, plus or minus the perceived differentiation because not all new drugs are by definition perceived as more convenient or effective. An important part of this strategy is therefore capturing the value and that value needs to be understood early in development (Gregson,

Sparrowhawk, Mauskopf, & Paul, 2005). Moreover, this pricing strategy highlights the fact that drug prices are not simply established through a cost-plus method, in which accumulated costs + a profit margin establishes the final price.

2.4 REIMBURSEMENT

In general, once a drug is registered by the regulatory authority, manufacturers can apply for reimbursement. Reimbursement is often controlled by governments, therefore controlling drug prices in a country. Acceptability of a price is often linked to the Incremental Cost Effectiveness Ratio (ICER) and budget impact (Gronde, Uyl-de Groot, & Pieters, 2017). A price offer is made based on an estimate of the volume of sales and the price at which the drug is reimbursed. Price negotiations may take place between the pharmaceutical company and the government (or reimbursement agency) to determine an acceptable price for each party. Reimbursement policies vary much more across countries than the standards required for marketing approval.

In the US for example, reimbursement is not controlled by the government due to the assumption that a free market will thrive competition and eventually lower prices. The effect in practice somewhat deviates from this perception due to skewed economic dynamics in this market structure where maximum profits are aimed by free price setting. As a result, prescription drug prices in the US are among the highest globally (Gronde, Uyl-de Groot, & Pieters, 2017).

Reimbursement in the NL

In order to understand the reimbursement procedure of drugs in the Netherlands, first a description follows of intramural and extramural drugs.

A general definition of intramural is 'within the walls/boundaries' and in the scope of healthcare refers to drugs being prescribed within the walls of a hospital. Intramural drugs are prescribed as part of a treatment or following a treatment in a hospital. Extramural drugs are directly acquired by a patient from a community pharmacy either with or without prescription of a general practitioner (Zorginstituut Nederland, 2018). Different procedures follow from these different types of classifications.

Extramural drug reimbursement

Extramural drugs qualify for reimbursement in the Netherlands once they are admitted in the drug reimbursement system (Geneesmiddelenvergoedingssysteem: GVS). This system is a so-called 'closed system'. The GVS is part of the national law on health insurance and consists of a list of reimbursed drugs. The Dutch National Healthcare Institute (Zorginstituut Nederland: ZiN) advises the minister of VWS (Volksgezondheid Welzijn en Sport) on the admittance of extramural drugs into the GVS. ZiN also takes into consideration the consul of the scientific advisory board (Wetenschappelijke Adviesraad: WAR) which consists of a maximum of 50 external independent specialists.

The extramural drugs in the system are then clustered into 2 sections:

Appendix 1A

♦ Consists of groups of mutually replaceable drugs. These drugs have a reimbursement limit.

Appendix 1B

♦ Consists of groups of mutually irreplaceable drugs. These drugs do not have a reimbursement limit.

Complementary to these two Appendices exist Appendix 2

Appendix 2

♦ Drugs that have been placed in either of the two sections can also be placed in appendix 2. This means there are additional conditions to reimbursement. This is the case when for example only part of a population group qualifies for reimbursement of a specific drug.

Reimbursement of intramural drugs

In the Netherlands, intramural drugs do not have a maximum reimbursement price. When an intramural drug is considered to be effective according to 'het Besluit zorgverzekering' (Bzv) it is automatically included in the basic insurance package. (Staatscourant 2017, nr. 47639) Therefore, this system is often referred to as an 'open system'.

However, intramural drugs with an extraordinarily high budget impact of more than 40 million and expected treatment costs of more than 100 million are not automatically admitted in the insurance package but are first put in a ''sluis''. (Kamerstukken II 2016/17, 29 477, nr. 420) The drug is then explicitly excluded from reimbursement and will only be admitted after assessment of The Dutch National Health Care institute (ZIN), successful price negotiations with the pharmaceutical company and agreements on proper use. The goal of this arrangement is to diminish financial risks by financially justifying the introduction of the drug in the reimbursement system.

Financial arrangements

In order to keep healthcare in the Netherlands affordable and accessible in the long term, the minister of VWS started negotiating on financial arrangements when considering reimbursement of drugs with a relatively high budget impact (VWS, 2017). The minister of VWS first negotiates on the price with the pharmaceutical industry before admitting the drug to the basic insurance package. New drugs that come to the market that can have a high impact on the healthcare budget are being evaluated on the following aspects:

♦ The budget impact in the Netherlands
♦ The price per treatment per patient per year
♦ The uncertainty on the prescription volume

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Table 1. Classification system

Annual Budget Impact		Costs per Patient per Year		Risk on Volume Increase	
Low	€0 - €10 mln	Low	€0 - €15.000	Low	1
Medium	€10 - €40 mln	Medium	€15.000 - €50.000	Medium	1-2
High	> €40 mln	High	>€50.000	High	>2

Using abovementioned system, new treatments are classified to their financial risk.

In addition, Zorginstituut Nederland will evaluate the drug and advise the minister of VWS on (direct) admittance in the basic insurance package or to use a conditional instrument such as a financial arrangement. Whether a drug definitively needs a financial arrangement is judged separately in each casus and each case has its own merits. Several indicators will be evaluated by the minister such as financial risk, budget impact, therapeutically added value, cost-effectiveness and whether the price is socially acceptable. (Kamerstukken II 2014/15, 29 477, nr. 328)

2.5 FINANCIAL RATIOS

Financial ratios are used for the analysis of the collected data and provide valuable information when comparing within a sample and across industries.

In order to understand to what extent net profits are reinvested into the development of new drugs, it is essential to comprehend how net profits are allocated within a company. Net profits are a company's total earnings and are calculated by taking revenues and subtracting the costs of doing business including interest, taxes and all other expenses. Subsequently, net profits can be paid out to shareholders as dividends or can be retained in the company. (Investopedia, 2018)

SG&A expenses

SG&A expenses are composed of all the commercial expenses of operation incurred in the regular course of business pertaining to the securing of operating income (Schonfeld & Associates Inc., 2018). SG&A expense generally includes advertising expense, commissions, engineering expense, marketing expense, selling expense including salaries of the salesforce and employee benefit expenses.

Dividend payout ratio

The dividend payout ratio is the ratio of the total amount of dividends paid out to shareholders relative to the net income of the company. This ratio provides an indication on how much of the yearly net income is returning to shareholders versus how much is being kept in the business. The ratio is calculated as the yearly dividends per share divided by the earnings per share. Alternatively, the

retention rate is the proportion of earnings that is being kept in the business as retained earnings. (Investopedia, 2018)

Dividend yield

The dividend yield is a financial ratio that indicates how much a company yearly pays out in dividends relative to its share price. Therefore, the dividend yield partially indicates the return on investment for a stock. The dividend yield can be calculated as the annual dividends per share divided by the price per share. (Maio, P. & Santa-Clara, P., 2015)

Retained earnings

Retained earnings are the profits that a company has earned less any dividends or other distributions paid out to shareholders. Typically, retained earnings are kept in the business for additional growth in areas such as working capital, capital expenditures, acquisitions and R&D. However, it may also be used to pay off debt or held in reserve for expectation of future losses. (Investopedia, 2018)

2.6 IMPULSE OF DIVIDEND PAYMENT DECISION

The sub-question of this thesis explores whether net profits are reinvested in the development of new drugs. Therefore, it is important to understand how net profits are allocated, whether net profits are retained in the company or are remitted to shareholders. When profits are remitted to shareholders they are remitted in the form of dividends. The dividend is the reward of shareholders for investing funds in the corporation. A recent study was conducted by Ariful Hoque to identify the impulse of dividend payment decision in pharmaceutical companies in Dhaka Stock Exchange. (Hoque, 2018) In this study the author developed a model in order to analyze the effect of the independent variables on the dependent variable.

The outcomes of the model in the abovementioned study show that profitability positively influences the dividend payment decision of selected companies but is however not statistically significant at 5% level. In addition, agency costs positively influence dividend payment decision, in the way that increased agency costs reduce agency conflict and will lead to increased profits. Firm's size, financial leverage and annual growth on the other hand negatively influences dividend payment decision and is statistically significant at 5%.

In a similar study on dividend policy of listed public companies in Malaysia, firm's size does have a significant positive impact on dividend policy (Yusof, 2016).

This thesis will explore dividend payments in relation to retained profits and the reinvestment in research and development.

3. RESEARCH METHODS

This chapter outlines the methodological framework used in this research study on the transparency of pharmaceutical companies. The data collection is explained, and the choices made are justified in order to describe the complete set-up of the study.

The aim of this research is to gain insight into which data presented by pharmaceutical companies support and justify the exertion of high prices leading to high budget impacts. In order to provide an answer to the main research question and all three sub-questions regarding this study, a framework was constructed containing multiple variables to be analyzed and compared between subjects and across industries.

3.1 STUDY DESIGN

For this research, a qualitative multiple case study was conducted in order to answer the main research question: *'To what extent do the economic data of pharmaceutical companies justify high budget impacts through the exertion of high drug prices?'* and the sub-question: *'To what extent are net profits reinvested into the development of new drugs?'.* By studying multiple cases, a better understanding will be established on the differences and similarities between the cases. Moreover, multiple cases allow wide exploring of research questions and theoretical evolution (Eisenhardt & Graebner, 2007) and the evidence created from a multiple case study is considered strong and reliable (Baxter & Jack, 2008).

3.2 STUDY POPULATION

The target population in this study essentially needs to consist of pharmaceutical companies that hold a prescription drug in their portfolio that generates a high budget impact through the exertion of a high price. As this may seem as a broad definition and a subjective matter, a purposive sampling technique is employed to select a relevant sample and to maximize efficiency and validity. To further define the scope and societal relevance, the pharmaceutical companies included in this study population consist of all companies that have a marketed drug in the Netherlands for which a financial arrangement was necessary for reimbursement to follow. Moreover, companies with a marketed drug in the Netherlands that was not directly reimbursed but first put in 'lock' (Dutch: sluis) were also included in the analysis although some overlap exists. This resulted in a time frame of 17 years as the first drug in the sample dates back to 2001 and the last to 2017.

The initial sample consisted of 21 pharmaceutical companies and 30 marketed drugs. The number of marketed drugs does not correspond with the number of pharmaceutical firms due to the fact that a number of firms have multiple marketed products with financial arrangements in the Netherlands.

The first two drugs date back to 2001 (Fabrazyme© and Replagal©) and were excluded from the sample due to unavailability of data which resulted in the drop-out of one pharmaceutical company (Transkaryotic Therapies Inc.).

In addition, three generic pharmaceutical companies were included in the study population and are merely used as a benchmark for the financial data. Hence, there were no drugs included for analysis from these generic companies.

See table 2 in Appendix A (p.54) for the entire study population.

3.3 FRAMEWORK SPECIFICATION

The aim of this research is to gain insight into what data presented by pharmaceutical companies support and justify the exertion of high prices leading to high budget impacts. Although multiple previous studies have tried to explain what factors in general account for the claim of a high drug price, little is known on the assessment of presentable data by multiple pharmaceutical companies and whether these claims can be considered valid. Therefore, this research can be considered exploratory.

In order to assess whether data presented by pharmaceutical companies justify the exertion of high prices leading to high budget impacts, a framework was constructed containing multiple variables to be analyzed and compared. All variables were included through an iterative process of literature and annual reports review. This framework consists of three main topics and is used in answering the research questions regarding this study.

1. Reporting
2. Variables
3. Financial

Data collection regarding the three topics included in the framework has been equally divided among the authors. However, the extent of detail into the analysis of the three topics differs depending on the sub-question.

REPORTING

The reporting part of this framework assesses the quality of transparency of the available information reported in the annual reports of pharmaceutical companies. First is being evaluated what statements are disclosed and into what detail they are presented. In addition, an evaluation takes place whether these statements are clear and socially acceptable. Each annual report is evaluated on criteria that can be found in these reports and resulted from an iterative process. As a result, a 'General Criteria Form' was constructed in MS Word and further details regarding the criteria points can be found in Appendix B (p.56).

This topic corresponds mainly to the second sub-question: *'How comprehensive, informative and socially acceptable are annual reports of pharmaceutical companies?'* and will therefore mainly be covered in that particular thesis.

As this research report covers the sub-question: *'To what extent are net profits reinvested into the development of new drugs?'*, the following criteria points are discussed in this research report:

- ♦ R&D/pipeline statements: Discussion of products in the pipeline & General description of the research and development process
- ♦ Profit policy: Dividend payouts and reinvestments in the business. Also, explanations regarding (expected) changes in the dividend policy
- ♦ R&D expenses: explanations regarding aggregated and disaggregated R&D expenses

Based on the reporting differences among pharmaceutical companies, a scoring system has been developed for the criteria points. Contrary to the other two research reports that cover the same research question, this research report focuses more thoroughly on the financial topic in order to provide an answer to the corresponding sub-question. Therefore, for an extensive review regarding the scoring system and remaining criteria points of the reporting topic, I would like to refer to the research report by F. Reitsma.

In this part of the framework, data is gathered from annual reports from the year in which the financial arrangement was negotiated in the Netherlands, and from the most recent year which was 2017. Moreover, data has been collected from the drugs in the sample. This data has been categorized and consists of variables that (combined) may contribute to the justification of a high price leading to a high budget impact. The collected variables can be grouped in the following categories:

Period of exclusivity

For each drug in the sample, patent expiry dates as well as EMA market approval dates have been gathered in order to establish how many years of patent protection are left when actual sales start to commence. This period represents the period in which the drug is on the market without competition and firms can therefore aim for maximum sales.

Additionally, data concerning the first year of EU sales are collected as this data might deviate from the EMA market approval data due to pricing/reimbursement hurdles.

Financial risk

Data is collected on what drugs are acquired instead of originated from in-house R&D. If a drug is acquired, the acquisition expenses are analyzed as well as in what development phase the drug is acquired. An overview is presented in Appendix C (p.60).

Third party relations

Data has been collected on drugs in the sample that were dependent on third party relations for the development and/or commercialization of the drug. An overview is presented in Appendix C (p.60).

Budget impact

For all drugs in the sample, the budget impact in the Netherlands has been established as these are all drugs with a financial arrangement in the Netherlands. Moreover, the DDD costs (Defined Daily Dosage) and treatment costs per patient per year are presented. These data are included for descriptive purposes rather than explanatory purposes.

Clinical risk

In this category, the clinical risk that a company bears at the moment of bringing the drug on the market (Y=T) has been analyzed. Factors that are indicative of such clinical risk are:

- The number of follow-on indications mentioned
- The number of drugs in portfolio with patent protection
- The number of potential candidates in the pipeline (phase 1,2,3)
- The number of EMA approvals in the period of analysis.

These factors may all contribute to the level of risk a company bears and therefore the price determination of a drug.

Product revenue ratio

The product revenue ratio provides information on the extent of revenue contribution per drug in the company. The product revenue ratio is calculated by dividing the revenue of the product with the total revenue of the company and is displayed in percentages. A high product revenue ratio might indicate that the pharmaceutical company is heavily reliable on one product. Revenue data from the most recent year has been gathered from the drugs in the sample as well as from the drug that provides the highest product revenue ratio in the company. The impact of the drugs in the sample leading to high budget impacts will be put in perspective with the drugs that contribute the most to the total company revenue in order to assess whether the impact is also visible within the company.

FINANCIAL

In this part of the framework, financial information is collected from all the companies in the sample. Since the first drug in the sample dates back to 2006, a period of 12 years of financial company data has been gathered to encompass the full financial scope of the sample. The data consists of relevant balance sheet items that are used in answering the thesis questions. Since this thesis answers the sub-question: *'To what extent are net profits reinvested into the development of new drugs?'* share information is gathered next to earnings and expenses to acquire a better understanding of how net profits are allocated within a company. Subsequently, key ratios have been established for data analysis and for comparison reasons.

3.4 DATA COLLECTION

This research used different methods for data collection including: literature review, document analysis and data extraction from financial databases.

LITERATURE REVIEW

A literature review was conducted to understand the topic of the research more thoroughly and to identify whether there is previous research done on the topic. This resulted in a theoretical framework in which the main concepts from the thesis question were addressed. In addition, brief summaries of known studies were discussed as well as contradictory perspectives. Literature was collected using the Google Scholar search engine. The search strategy was developed using combinations of search terms relevant to the specific subtopics. Once the relevant articles were selected, bibliographies of these articles were searched for additional references. In addition, literature provided by the Erasmus University in the course 'Pharmaceutical Pricing and Market Access' was used in the literature review. Articles regarding the reimbursement regulation in the Netherlands were found using institutional government websites such as

https://zoek.officielebekendmakingen.nl/zoeken/parlementaire_documenten and https://www.zorginstituutnederland.nl/.

DOCUMENT ANALYSIS

The document analysis is done for the 'reporting' and 'variables' part of the framework and is equally divided by the authors of the three sub-questions. First, the three authors collected all types of data for one and the same pharmaceutical company to ensure consistency in the way of data collection. For

the 'reporting' part of the framework, data is gathered from the most recent (2017) annual report published by the pharmaceutical company, since this would be the most informative for how these companies operate nowadays. For the 'variables' part of the framework, data is gathered from annual reports either on a form 10-k required by the U.S. Securities and Exchange Commission (SEC) that gives a comprehensive summary of a company's financial performance and include audited financial statements. In the absence of data in the annual reports, the company's website has been used to acquire data. Moreover, data is used from the European Medicines Agency (EMA) and data concerning the category 'budget impact' were found on institutional government websites such as https://www.zorginstituutnederland.nl/ and https://www.medicijnkosten.nl/. Statistical analysis was performed using STATA software, version 14 (StataCorp). The data was categorized, edited, as well as organized in MS Excel for analysis.

FINANCIAL DATA EXTRACTION

The financial company data was collected using a financial database 'ThomsonOne' of which access has been granted through the Erasmus Data Service Centre (EDSC). ThomsonOne contains financial data from annual reports, as well as data about mergers and acquisitions. In the case of supplementary data, or in the case of unavailable data, SEC reports on form 10-k were used to acquire missing data and were found on the company website or the SEC website. Additional industry benchmark data has been collected through 'Wharton Research Data Service' (WRDS). Industry benchmark data was available over the period 2006-2015. Moreover, Fama-French 49 industries classification has been used for comparing industry medians. Statistical analysis was performed using STATA software, version 14 (StataCorp). The data collected was then edited, as well as organized in MS Excel for analysis.

3.5 DATA ANALYSIS

As discussed, a framework was constructed containing multiple variables to be analyzed and compared within subjects. The collected data is gathered and exported into MS Excel and MS Word for analysis. These were iteratively developed, ensuring that all relevant variables were included. The analyses, just as the framework, consists of three parts. The financial data was quantitatively analyzed using MS Excel for a 12-year period between 2006-2017. The data is analyzed and compared within the sample, as well as outside the sample for benchmarking reasons. Key ratios were used to acknowledge valuable perspectives between companies and to answer the sub-question regarding this thesis. The reporting data was qualitatively analyzed, based on annual reports from 2017. The data regarding the relevant variables was both quantitatively and qualitatively analyzed. Ultimately, the three parts of the analyses were combined, and patterns were matched in order to derive the most valid results.

3.6 VALIDITY & RELIABILITY

Explicit scrutiny is needed to safeguard validity and reliability. To ensure internal validity, an Excel database has been developed for the Financial data and indicator variables in order to make pattern-matching possible. In addition, the data was analyzed using statistical software. Moreover, the general criteria form explicitly refers to page numbers in the annual reports which indicate that results can be confirmed by others. This also adds to the reliability of the study, namely whether replications of the study arrive at the same findings. Qualitative research is however time and context dependent which makes it more challenging to replicate it exactly. Reliability is ensured by using consistent processes which was done when analyzing and collecting the data.

External validity concerns the generalizability of the research, therefore setting an appropriate scope for generalizing study results. This is inherent to the study design itself and follows from the use of replication logic (e.g. finding consistent patterns in the data) in multiple cases which was also done in the Excel database. To ensure consistency in the data collection, all three authors collected data for one pharmaceutical company and findings were compared afterwards. This sets an appropriate scope for generalizing study results.

Moreover, outcomes of the study must not result from subjective judgements from the researcher. Therefore, it is important to establish correct operational measures for the concepts being studied and this can be tackled by triangulation of results.

To ensure triangulation of findings, data was compared between the different authors of this study and verified by each other in order to minimize the possibility of bias.

4. RESULTS

In this chapter, the most important and most striking findings will be presented and guided by the research questions and theory. Reflection and further interpretation on the results follow in the Discussion chapter. The results are organized following the three central topics as discussed in chapter 3: reporting (1), variables (2), financial (3).

The entire study population consists of 23 pharmaceutical companies and 28 marketed drugs. Three generic companies (Mylan, Teva & Sun Pharmaceuticals) are merely included for the analysis of financial company data and are therefore only included in the financial part of this chapter. Median figures are provided in addition to the mean as the median figure provides a more accurate representation in the case of outliers.

All drugs in the sample were approved by both the FDA (U.S. Food & Drug Administration) and EMA in the period 2006-2017. 7 out of 28 marketed drugs have received the orphan drug designation. Three companies, Genzyme, Intermune & Aegerion, have been acquired by respectively Sanofi, Roche & Novelion in the period of analysis. 9 out of the 28 drugs had a different originator than the one bringing the drug on the market.

The entire study population can be found in Appendix A (p.54).

4.1 REPORTING

In this part of the results, the reporting topics are discussed that are most relevant in answering the sub-question: *'To what extent are net profits reinvested into the development of new drugs?'*.

Profit policy

All pharmaceutical companies in the sample except for Roche stated their profit policy in the annual reports, indicating whether dividends were paid out to shareholders or whether profits were retained in the business. Expected changes in the amount of cash dividends paid were also reported in the cases where dividends were paid out to shareholders. This information is relevant for the return on investment shareholders can expect annually and is therefore included. However, no additional statements regarding the allocation of retained profits were provided, therefore it is unclear what share of net profits are reinvested into the development of new drugs. No additional non-financial information concerning profits or shareholder payouts was provided by these pharmaceutical companies. Therefore, a motivation for the choice of paying out dividends or on the other hand retaining profits in the business for reinvestment was lacking in all the annual reports. Such a motivation for the choices made by the company would perhaps provide more information whether retained profits are reinvested into the development of new drugs or are spent elsewhere.

R&D/pipeline statement

In all annual reports, products in the pipeline were discussed as these products will account for future revenue. In addition, most companies gave an explicit explanation of the necessary steps in the research and development process and discussed regulations for market authorization. However, this was not the case in the reports of Otsuka and Daiichi Sankyo as these companies focused more on key performance indicators (KPI's), such as in-house drug discovery percentage, R&D-to-sales ratio and the amount of late-phase pipeline projects. These differences in reporting might have to do with differences in expectation of their shareholders as both of these companies mostly operate in Japan. Therefore, the development process is explained except the link to profits is missing.

R&D expenses

All companies reported R&D expenses in their annual report. However, in seven cases, only aggregated R&D expenses were presented which provides a limited view. Other companies disaggregated costs based on product (segment), organizational silos or development phases, ranging from 2 to 13 items. Two relatively smaller companies with only 2 products in their portfolio showed the most detailed R&D expense overview. It is therefore questionable what determines how detailed a company presents its R&D expenses in the annual report. The disaggregated R&D expenses would allow us to see what percentage of the expenses is purely allocated to the development of new drugs. It could for example be the case that salaries of R&D personnel are included in these expenses and therefore only an aggregated view presents limited information.

The lack of sufficient non-financial information relating to retained profits, shareholder payouts and R&D expenses make it questionable whether there exists a certain policy regarding R&D reinvestments and the presence of a correlation between profits and R&D expenses. Therefore, key financial ratio's may provide more insights regarding the ratio between profit and R&D.

4.2 VARIABLES

This part of the results displays the most striking findings from the annual reports review regarding the drugs in the sample. Data concerning drugs in the sample are collected from the year in which the financial arrangement started and from the most recent year in the sample. These data have been categorized and the most important findings are presented by category in this part of the chapter.

First, descriptive statistics regarding the budget impact in the NL are shown in table 3.

Table 3. Descriptive statistics of the budget impact in NL

| *Total number of drugs*					
n= 28					
(In €)	*Mean*	*95% CI*	*Minimum*	*Maximum*	*Median*
Treatment cost per patient per year	123,308.4	(60,434.32 – 186,182.5)	1,762.95	577,864.3	43,572.08
Budget impact NL	37,600,000	(21,100,000 – 54,000,000)	850,000	165,000,000	25,000,000
DDD[1] cost	386.7	(217.44 – 556.14)	4.83	1583.19	251.29

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[1] Defined Daily Dosage

Period of exclusivity

Table 4 in Appendix C (p.58) displays all drugs in the sample with their corresponding patent expiry date and EMA market approval date.

A prominent finding in this research concerns the period of exclusivity on the market. To be more precise, the time left between EMA market approval and patent expiry. The mean of the time left between market approval and patent expiry regarding the 28 drugs in the sample was 11.5 years (95% CI, 10.1 – 12.9) and the median was 13 years (range, 3 – 16). In Figure 6, a scatterplot displays the dispersion among the pharmaceutical companies. Only 6 out of 28 drugs have less than 8 years of patent protection left.

The possibility exists however, that there might be significant time between market approval that has been granted and actual realized sales due to pricing and reimbursement hurdles. Therefore, additionally the time between the first year of sales realized in the EU and patent expiry has been analyzed in the sample. The results showed the exact same mean and median figures because the year of first sales in the EU were the same as the year of market approval. In a few cases, the drug had been sold in a previous year, however not in the EU.


Figure 6. Period of exclusivity left after market penetration
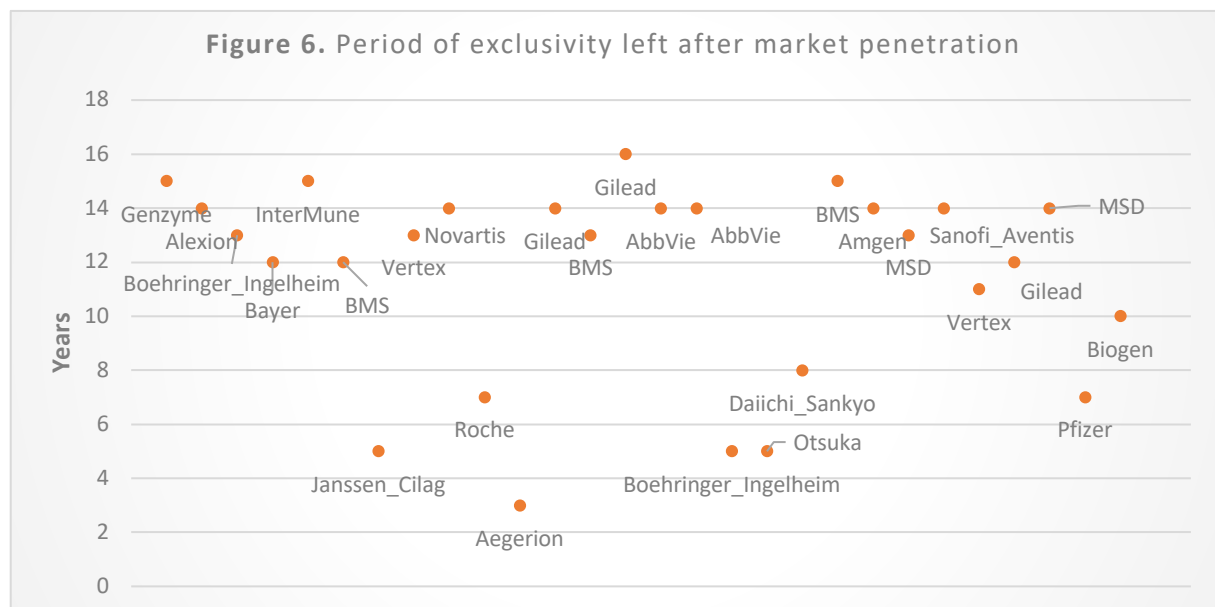
Product revenue ratio

In order to evaluate the financial impact on the company's revenue, product revenue ratios have been analyzed for the drugs in the sample. Data has been gathered from the most recent year, 2017, on the revenue contribution of the 28 products in the sample to the total revenue realized. In addition, the revenue of the product with the highest revenue has been compared to the total revenue realized. Due to unavailable data, two drugs (Myozyme & Esbriet) were excluded resulting in 26 drugs to be analyzed.

The mean value of the product revenue split of the 26 drugs in the <u>sample</u> was 15.3% (95% CI, 7.0% - 23.7%) and the median was 6.9% (range, 0.2% - 88.6%).

The mean value of the revenue split of the product with the <u>highest revenue</u> was 27.4% (95% CI, 18.5% - 36.3%) and the median was 17.2% (range, 3.9% - 88.6%).

Figure 7 displays the dispersion of the product revenue ratios. The Y-axis displays the product revenue ratio of the drugs in the sample and the drugs with the highest revenue for each pharmaceutical company. The X-axis displays the total number of products the pharmaceutical company holds in its portfolio.

Figure 7. Dispersion of product revenue ratios vs. # of products in portfolio
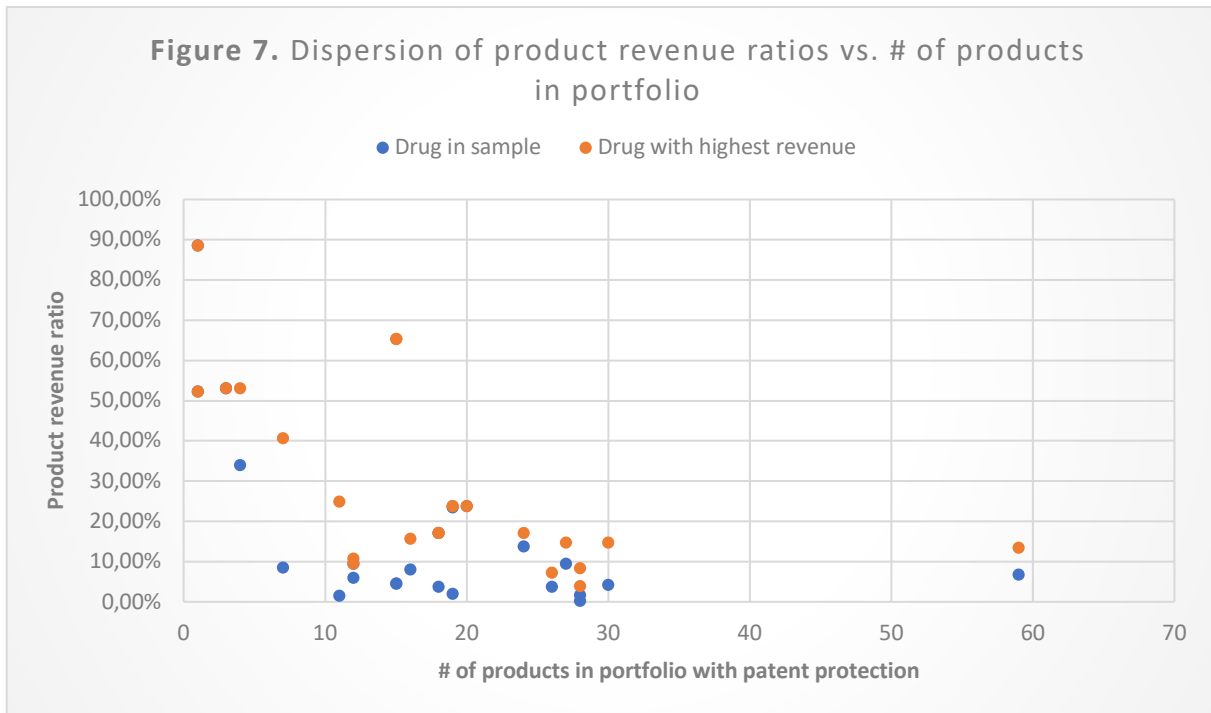
From the figure it is noticeable that in the case one of the companies holds a drug with a relatively high impact on the total revenue of that company, it holds a relatively low number of products in its portfolio. The next chapter elaborates on these results. Furthermore, 6 out of the 26 drugs in the sample were accountable for the highest product revenue ratio in their company in 2017 and are displayed in figure 8. For the more recently launched drugs in 2015 this means they have become the top selling drug in their company in approximately 2 years' time.

Figure 8. Drugs in sample with the highest revenue contribution in their company
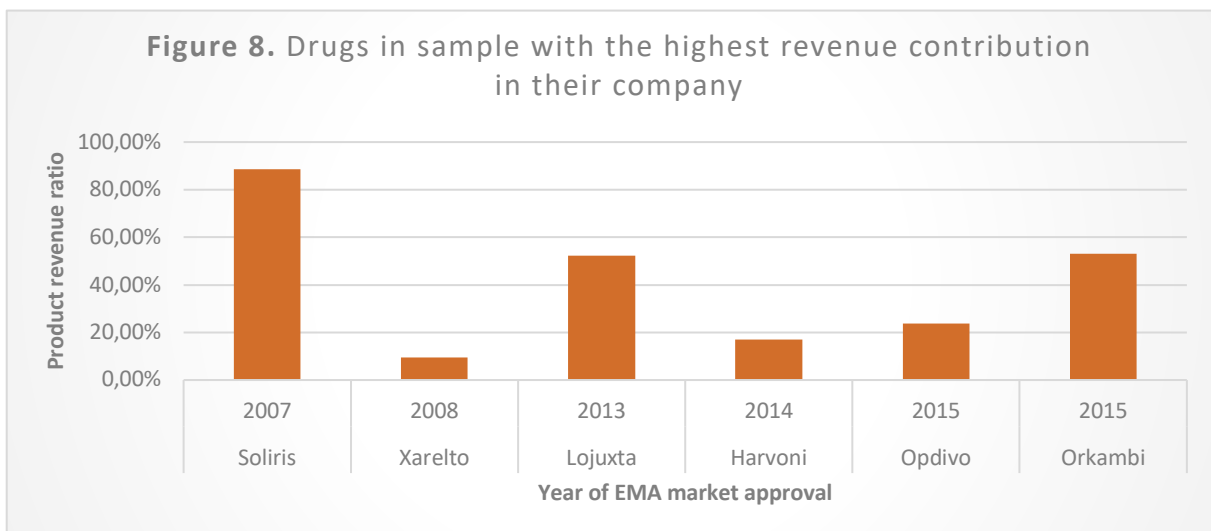
Clinical risk

The level of risk that is accompanied with the launch of a new drug can contribute to the price determination of a drug. It might however be the case that not all companies endure the same levels of risk. An objective is to determine whether all companies endure the same risk when bringing a drug on the market. It is however quite challenging to determine the exact measure of clinical risk endured by companies as not all information regarding the development of a drug is publicly displayed. The different levels of clinical risk companies endure may contribute to the social acceptance and understanding of the exertion of a high drug price.

In figure 9, data concerning the number of products in phase 3 have been gathered from the year in which the product was launched, and the financial arrangement started. This would provide a fair view on future products to be added to the portfolio at the time of product launch.

In the figure, an upward trend is visible indicating that the number of phase 3 drugs a company holds may increase with the global revenue of the company.

Figure 9. Global revenue vs. Number of phase 3 drugs
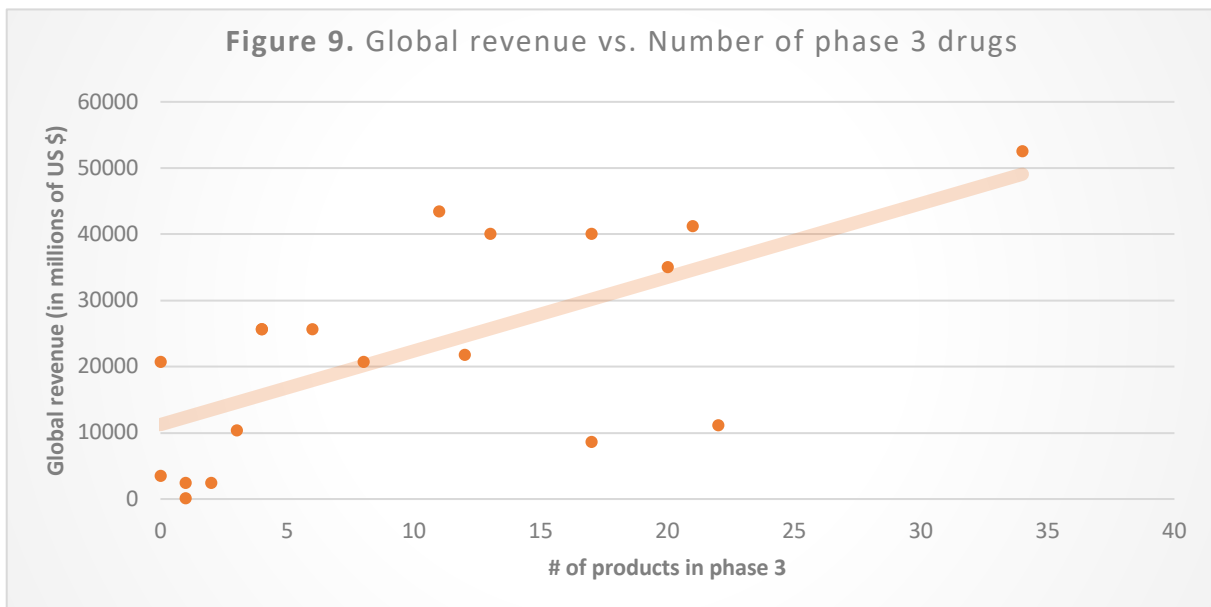
4.3 FINANCIAL

This part of the results displays the most striking findings regarding the financial company data that has been collected from financial databases and annual reports. The data has been analyzed and the most important key ratio findings are presented. Boehringer Ingelheim has been excluded in the financial analysis due to unavailable data for the selected period in financial database ThomsonOne. Therefore, the total list of companies included in the financial analysis over the period 2006-2017 is as follows:

Table 5. Companies included for financial analysis

2006-2017					
Company name	*Sample*	*Generic*	*Company name*	*Sample*	*Generic*
1. Abbvie	√		12. Johnson & Johnson	√	
2. Aegerion	√		13. Merck	√	
3. Alexion	√		14. Mylan		√
4. Amgen	√		15 Novartis	√	
5. Bayer	√		16. Otsuka	√	
6. Biogen	√		17. Pfizer	√	
7. BMS	√		18. Roche	√	
8. Daiichi Sankyo	√		19. Sanofi	√	
9. Genzyme	√		20. Sun Pharmaceuticals		√
10. Gilead	√		21. Teva		√
11. Intermune	√		22. Vertex	√	

Six relevant and comparable industries have been used in the analysis of key ratios. Industry level data has been collected through Wharton Research Data Service and was available for the period 2006-2015.

The three generic companies (Mylan, Sun Pharmaceuticals & Teva) together were accountable for 45% of the top 10 revenue in the generics industry in 2016 (Statista, 2016).
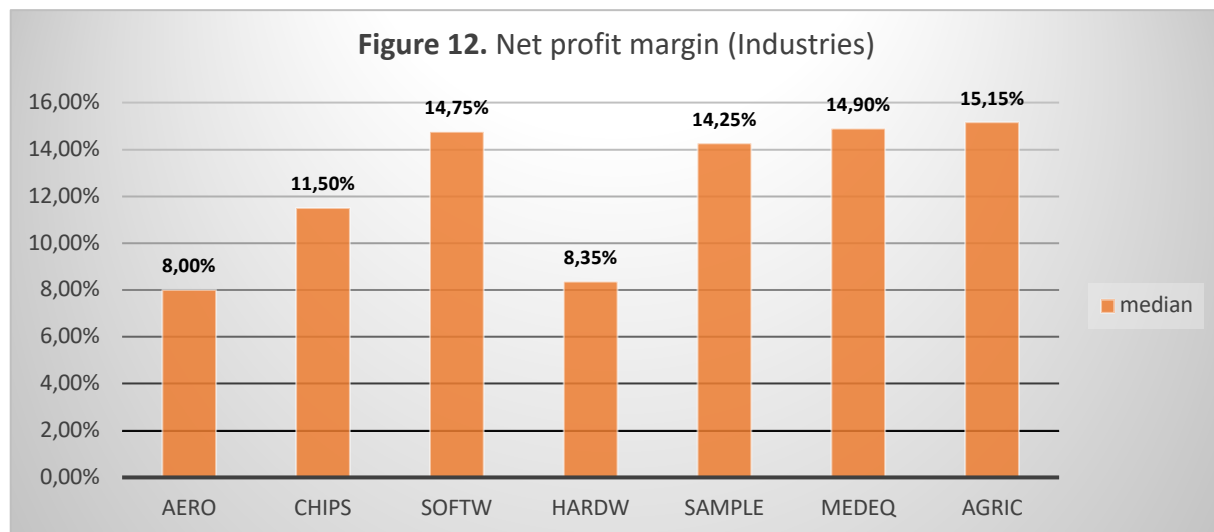
Profit margin

The mean profit margin in the sample was -4.6% (95% CI, -15.8% - 6.7%). Three companies in the sample, Aegerion, Intermune and Vertex have not been profitable during the period of analysis (except for Vertex in 2017) resulting in overall negative profit margins. Two of those companies (Aegerion and Intermune) have been acquired by another pharmaceutical company. One observation has been dropped from the data due to the fact it was an extreme outlier resulting in inaccurate findings. The median profit margin in the sample was 14.3% (range, -630.3% - 76.3%). The wide range displays the diversity of the different type of companies present in the sample. Relatively low/negative profit margins are displayed by starting biotech companies such as Aegerion and Alexion. The most prominent finding among companies in the sample was concerning Gilead Sciences. The mean profit

margin of Gilead was 30.4% (95% CI, 16.7% - 44.1%) and the median profit margin was 37.0% (range, -39.3% - 55.5%). Figure 10 and 11 in Appendix C (p.59) display more information regarding the net profit margins in the sample.

The industry has been put in perspective by comparing it with other relevant industries and can therefore help in better understanding the magnitudes of the results. The six industries that are used for comparison are:

- ♦ Aircraft
- ♦ Chips (Electronic Equipment)
- ♦ Software
- ♦ Hardware
- ♦ Medical equipment
- ♦ Agriculture

The first five industries are comparable to the pharmaceutical industry due to their capital-intensive structure, with medical equipment being the closest relatable. However, one major feature that still sets the pharmaceutical industry apart concerns the safeguarding of public health. The social welfare costs of producing a bad drug might be higher than when developing bad software due to the public health effects. Therefore, the Agricultural industry has been added for comparison reasons as this industry has similar features and risks concerning both R&D as public health to be cautious about.


Figure 12. Net profit margin (Industries)

Three out of six industries display a higher median net profit margin than the sample profit margin (Wharton Research Data Service, 2006-2015).

Dividend payout ratio

The mean dividend payout ratio in the sample is 51.5% (95% CI, 34.6% - 68.5%) and the median dividend payout ratio in the sample is 35.2% (range, -21.4% - 1914.3%). This automatically implies that the median retention rate of the sample was 64.8%, implying profits being retained in the company usually for growth of the business. The payout ratio will be negative in the case when there has not been any profit, but dividends are still being paid out. When the payout ratio exceeds 100%, the amount of dividend paid out exceeds the amount of net income.

Figure 13 Displays the median dividend payout ratio of the companies in the sample during the 12-year period on the X-axis, and the global revenue of those companies on the Y-axis. In this figure an

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upward trend is visible regarding the dividend payout ratio of a company and the size of the company (measured in terms of revenue) which is in compliance with the theory (Yusof, 2016).

Figure 13. Global revenue vs. Dividend payout ratio
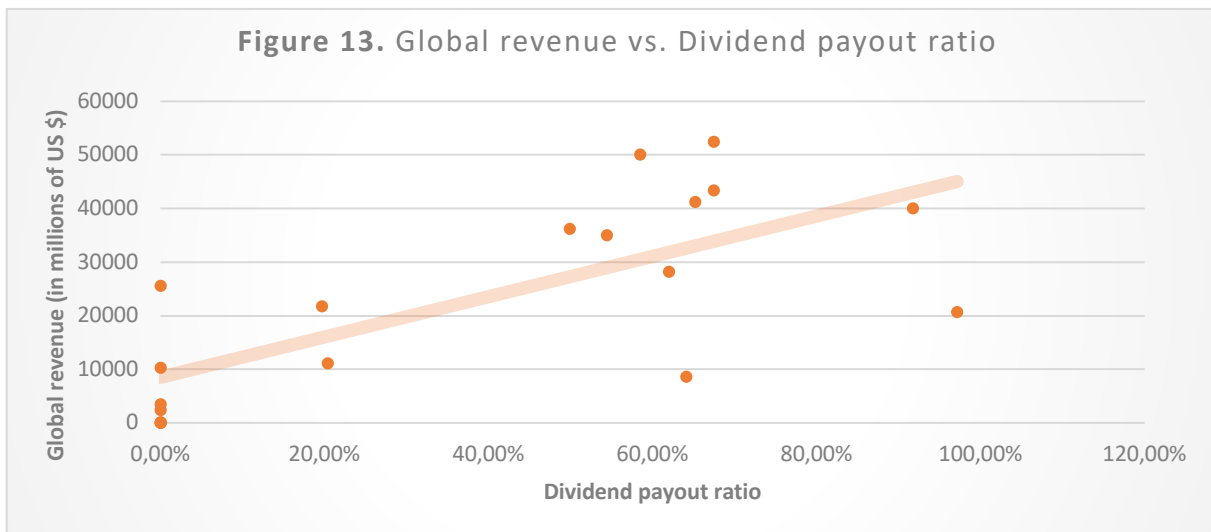
Remarkable are the median dividend payout ratios of Bristol-Myers Squibb and Merck & Co which exceed 90%, respectively 97.1% (range, 23.3% - 255.7%) and 91.7% (range, 26.8% - 542.9%). Those companies are among the top 13 pharmaceutical companies in the world regarding revenue (Statista, 2016). When taking into account other industries, the median dividend payout ratio in the sample exceeds all other industries (Wharton Research Data Service).

Figure 14. Dividend payout ratio
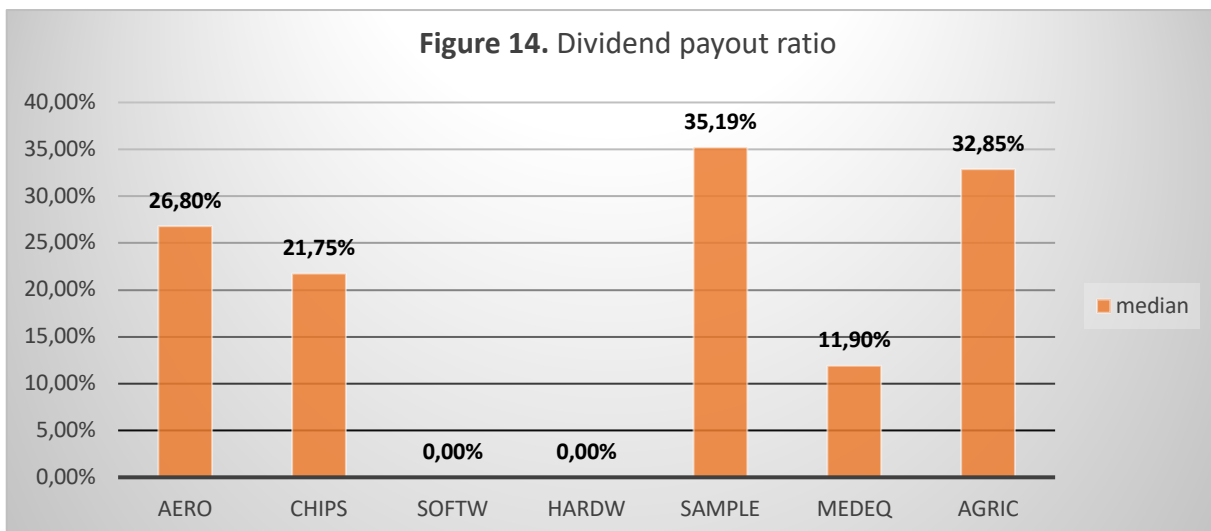
In addition, the median dividend yield in the sample was 2.4% (range, 0% - 9.1%) which in comparison with other industries provides the highest yield. For more information, see figure 15 in Appendix C (p.60). The dividend yield is effectively the return on investment for a stock. Therefore, the yield represents the attractiveness of a stock for shareholders, yet high dividend yields may come at the cost of growth potential. Every dollar a company is paying in dividends to its shareholders is a dollar that is not reinvested in itself, for example the development of new drugs.

Net profit/R&D

There exists no direct cash flow movement from net profits to what is being spent on R&D. Therefore, finding a direct correlation between net profits and R&D is merely possible through company statements made public but the previous section has already shown no additional non-financial statements have been made regarding profit allocation in the company. The profit/R&D ratio displays the ratio between net earnings after deductions of all expenses and what is being spent on R&D. The mean profit/R&D ratio in the sample was 97.2% (95% CI, 77.3% - 117%) and the median profit/R&D ratio in the sample was 95.9% (range, -880.1% - 807.4%). This indicates that roughly an equal amount of money is spent on R&D as is left as net earnings after deduction of all expenses in the 12-year period.

Figure 16. Net profit/R&D
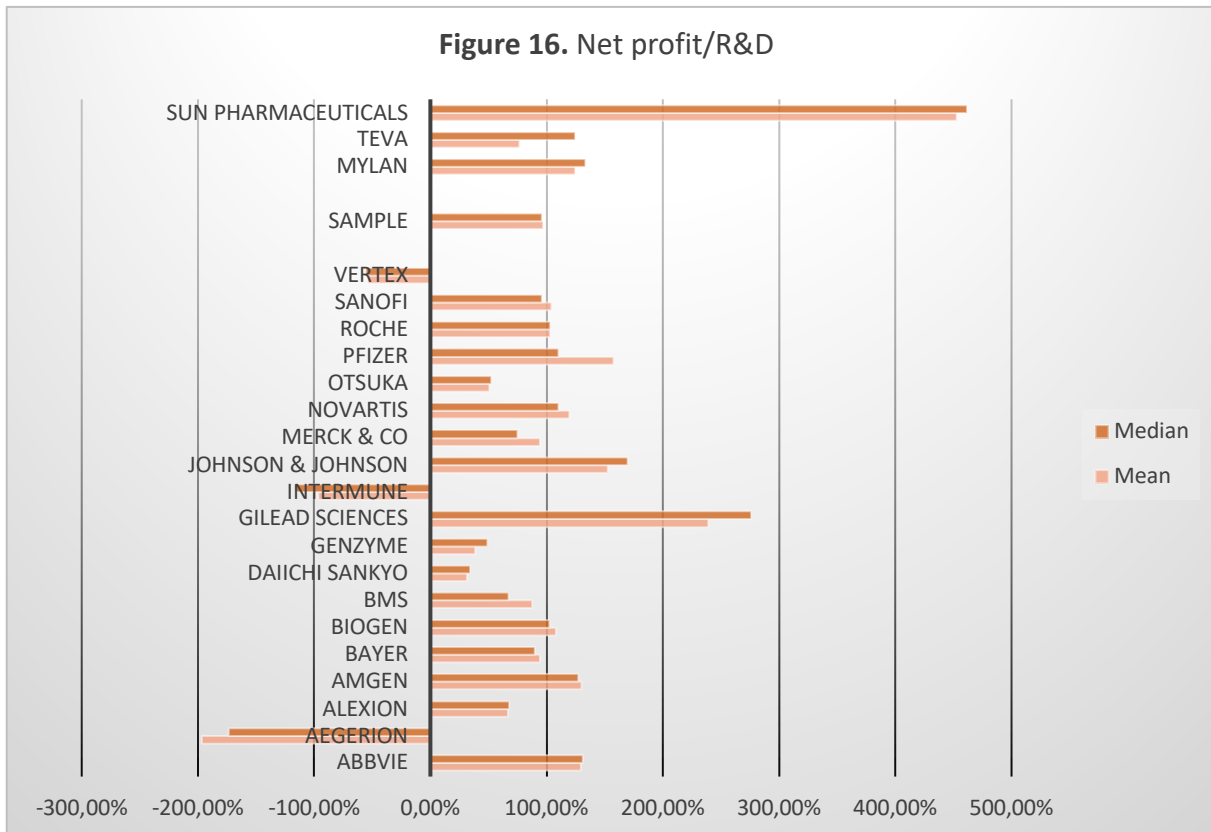
As can be seen in figure 16, the companies that have not been profitable yet display a negative net profit/R&D ratio. One remarkable observation is the median net profit/R&D ratio of Gilead Sciences which was 276% (range, -310% - 600%) over the analyzed period. This indicates that the amount of net profit in the 12-year period was nearly three times the amount that has been spent on R&D.

The generic companies all displayed a median net profit/R&D ratio that exceeds 100%. This aligns with the theory and can be explained by relatively low R&D expenses, which is common for generic companies, rather than unusually high profits.

The relatively low amount of R&D expenses of generic companies is also visible when linking R&D to EMA approvals.
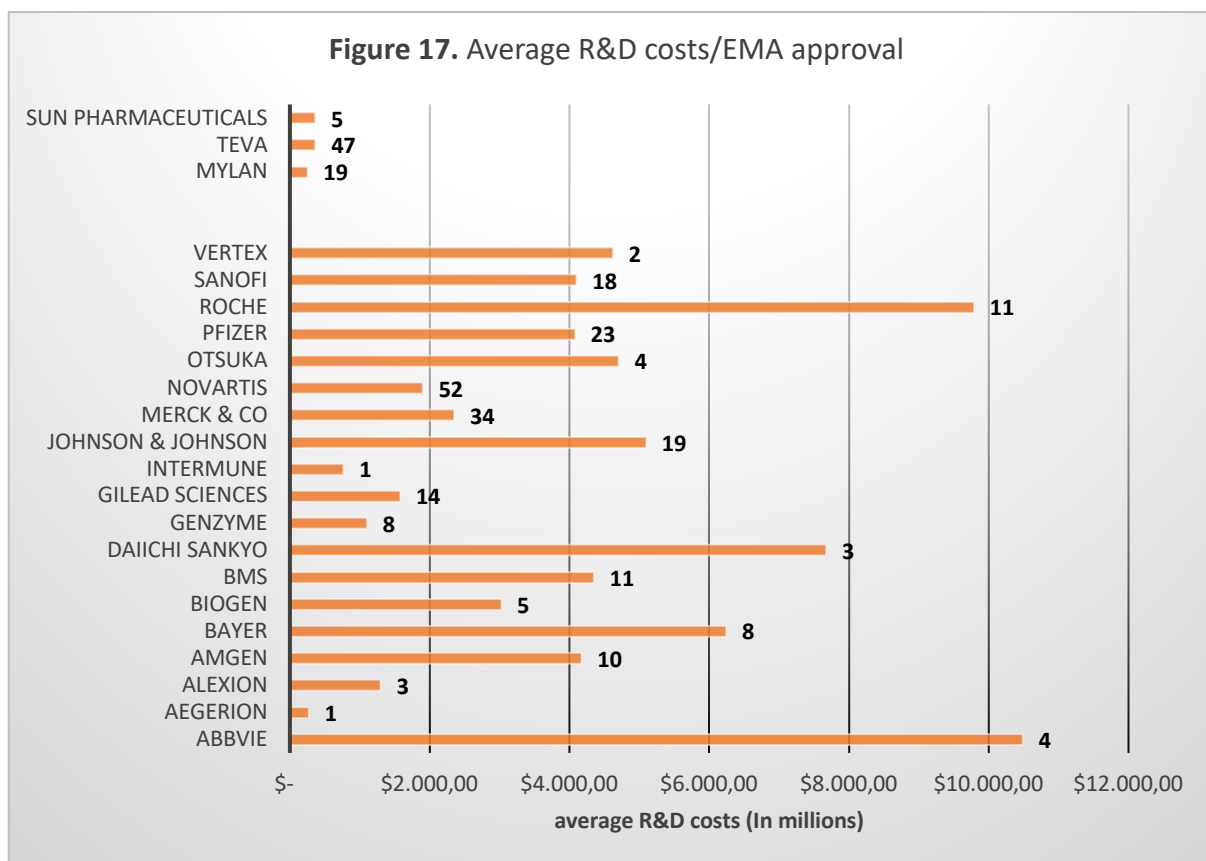
Figure 17. Average R&D costs/EMA approval

Figure 17 displays the average R&D costs per EMA approval and the number of EMA approvals obtained in the 12-year period. When considering the three generic companies, the relatively low average costs per EMA approval and the relatively high number of approvals illustrate the significant differences between innovator firms and generic firms with respect to R&D. Remarkable are the high number of EMA approvals of Novartis and the relatively low average R&D costs per EMA approval. Especially considering all Novartis' approvals were innovator drugs meaning no generics and no biosimilars. Novartis displayed an average R&D cost of $1900.79 per EMA approval with in total 52 approvals in the 12-year period. Only 5 companies displayed a lower average R&D cost per EMA approval, however none of those companies obtained more than 14 approvals in that period. On the other hand, AbbVie displayed an average R&D cost of $10488.87 with only 4 approvals in the 12-year period.

Table 6. Extreme findings regarding the number of EMA approvals relative to the average R&D costs per approval

| *Company*	*# of EMA approvals*	*Average R&D costs per approval (in millions)*
Novartis	52	$1900.79
AbbVie	4	$10488.87

These figures should however be interpreted with caution as significant differences exist between biological and non-biological drugs. The R&D costs accompanied with the production of biological drugs can be significantly higher.

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Figure 18 shows the average R&D costs per EMA approval over the 12-year period regarding all companies in the sample. From this figure, no evident upward or downward trend is visible which may indicate R&D productivity may not be declining in the way theory suggests. The next chapter elaborates on this matter.

Figure 18. Average R&D costs/EMA approval 12-year period
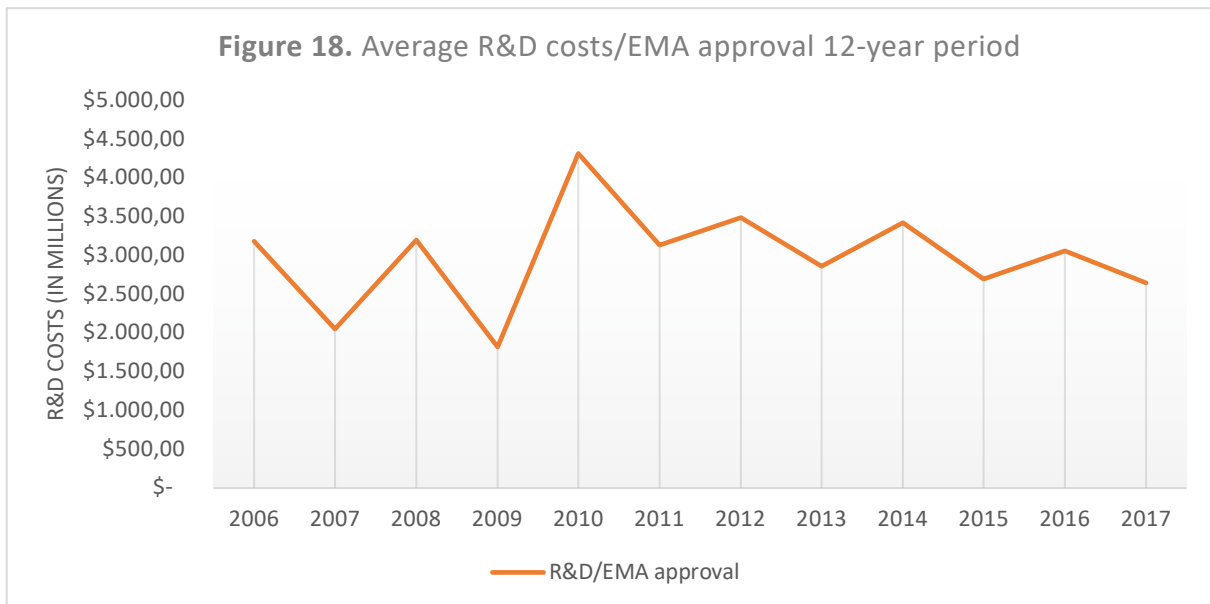
Operational ratios

The median R&D/Revenue ratio in the sample was 16.5% (range, 0% - 5335%) and the median SG&A (Selling General & Administrative)/Revenue ratio was 28.3% (range, 0% - 3518%). This implies that over the 12-year period, when considering the division in operational ratios in the sample, the R&D/Revenue ratio comprises 37% as opposed to 63% of SG&A/Revenue as is displayed in figure 19.

Figure 19. R&D vs. SG&A
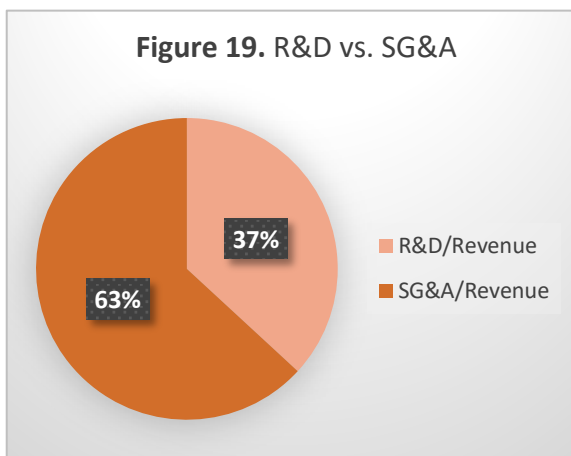
According to data provided by the New York University Stern School of Business this division in the entire global pharmaceutical industry is considerably different.

In their dataset, 952 biotechnological pharmaceutical companies are included (NYU Stern School of Business, 2018) and display the following division with respect to R&D and SG&A expenses.

Figure 20. R&D vs. SG&A
Pharmaceutical companies n=952

- R&D/Revenue
- SG&A/Revenue
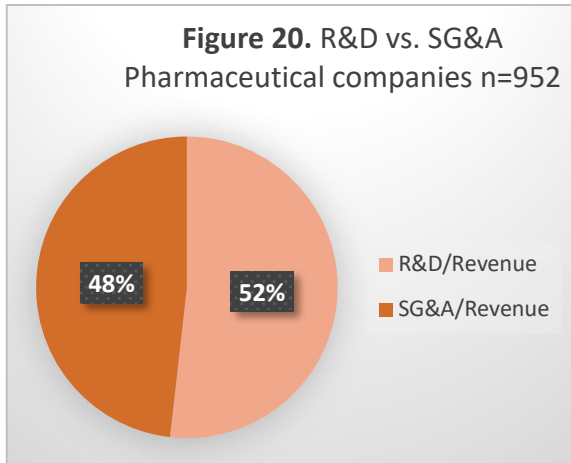
Obviously, the number of firms in this sample is significantly lower than the number of firms in the dataset provided by the NYU Stern School of Business. However, 8 out of 10 pharmaceutical companies in the top 10 ranked by revenue are included in this sample.

Acquisition of business

Three out of 19 companies in the sample (Gilead Sciences, Alexion and Aegerion) displayed an acquisition/R&D ratio that exceeds 100% indicating that more money has been spent on acquisition of business in the 12-year period than was invested in Research & Development. The relatively high ratios presented by two of the generic companies again illustrate the low levels of R&D expenses generic companies bear rather than great amounts being spent on acquisition of business.

Figure 21. Accumulated Acquisition of business/Accumulated R&D

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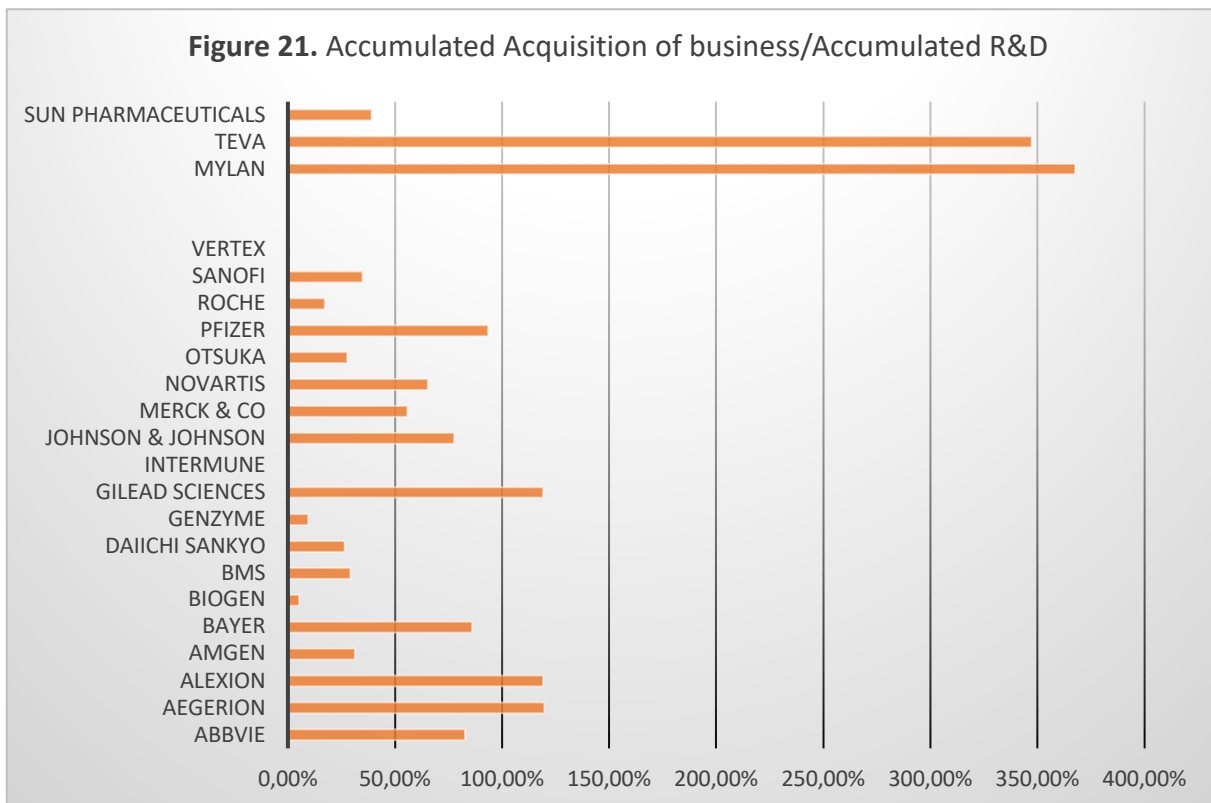
Retained earnings

Every dollar of retained earnings means another dollar of shareholders' equity or net worth. Therefore, the balance post *retained earnings*, and its development over the years, can indicate to what extent a company is growing and to what extent funds are being added to the company reserves, thereby adding to the wealth of the company.

Figure 22.1 displays the development of the retained earnings balance for the three smallest companies in the sample with respect to revenue during the 12-year period. Not all companies in the sample therefore show positive developments with regard to their wealth. Downward trends are visible indicating that these companies that have introduced a medicine with a high financial risk are showing decreasing and negative retained earnings. This may come down to capital depreciation due to ongoing losses of the company. It is important to notice that two out of these three companies have been acquired by another pharmaceutical firm, making it questionable whether these companies would have sustained on their own.

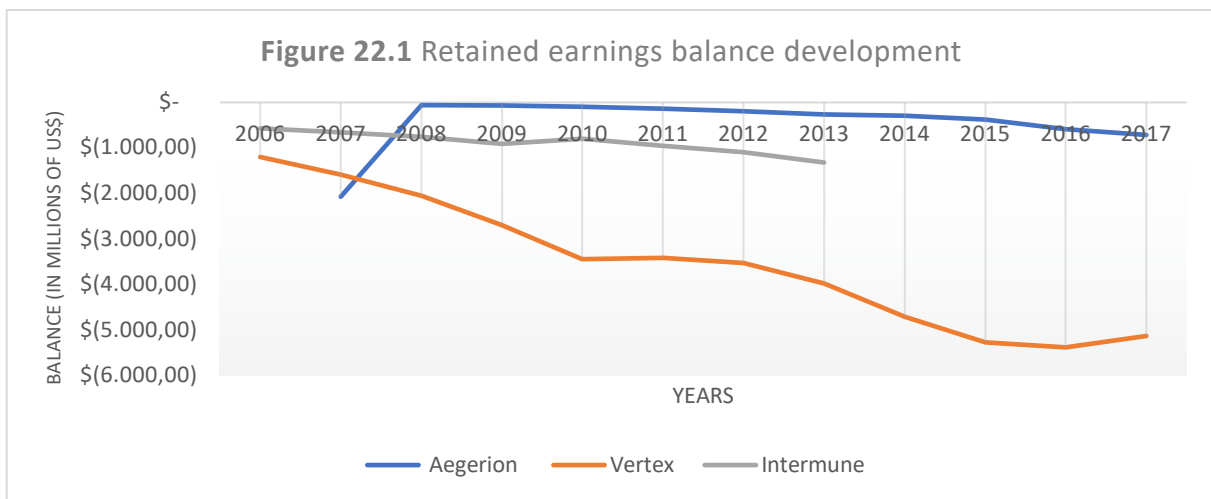Figure 22.1 Retained earnings balance development

Figure 22.2 displays the development of the retained earnings balance for the three biggest companies in the sample with respect to revenue during the 12-year period. All of the three firms show the retained earnings balance keeps growing, therefore enabling an even bigger expansion of the company operations.

Figure 22.2 Retained earnings balance development
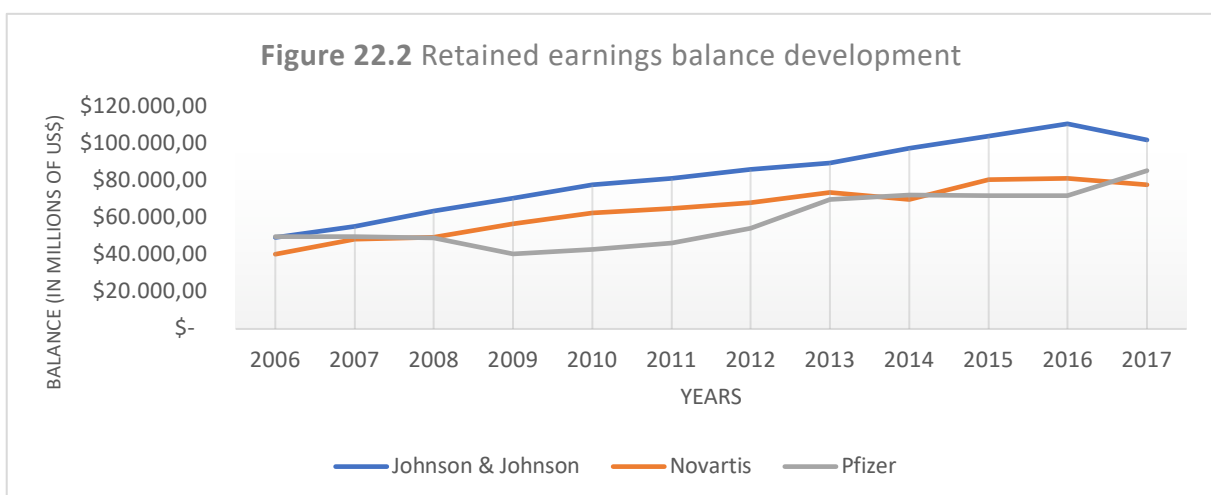
Retained earnings spending

As has been discussed in the theoretical framework, net profits can either be paid out as dividends to shareholders or can be retained in the company. Net profits that are retained in the company are most often used for growing the business, therefore accumulated retained earnings spending can provide information on the magnitude of expansion of the company. The ratio retained earnings spending/R&D can provide a clear image on the division of expenses with regard to these two balance sheet items.

In the sample, Amgen and Gilead Sciences both displayed a ratio exceeding 100% indicating more has been spent from retained earnings in the 12-year period than has been invested in R&D.
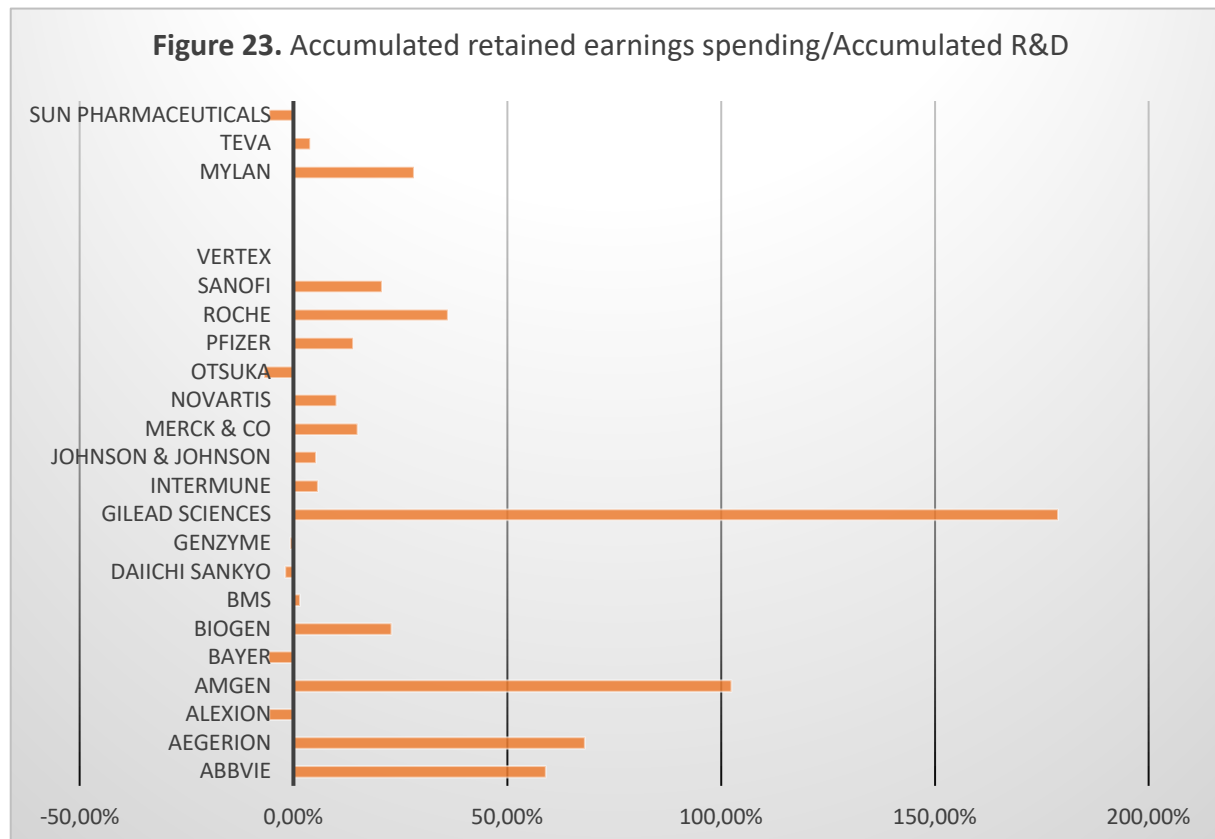
Figure 23. Accumulated retained earnings spending/Accumulated R&D

As the sub-question regarding this thesis tries to explain whether net profits are reinvested into the development of new drugs, it might be interesting to explore how retained profits are being spent in a company and how those expenses relate to R&D expenses. Table 7 shows for the two companies that display ratios exceeding 100%, what percentage of retained earnings during the 12-year period were spent on share repurchases. This is important to include as this means additional yield for investors and entails a relatively large proportion when comparing with R&D.

Table 7. Percentage of retained earnings spent on share repurchases

Company	Accumulated retained earnings spending (in millions of US $)	Accumulated spending on share repurchases (in millions of US $)	% of retained earnings spent on share repurchases
Gilead Sciences	39482.17	38961.68	**98.68%**
Amgen	42748	38246	**89.47%**

The results indicate that a substantial amount of retained earnings spending is spent on the repurchasing of shares. The next chapter elaborates on this matter.

5. DISCUSSION

In this chapter, the most striking results are interpreted, discussed and compared with the literature upon which the research questions will be addressed (§5.1). Furthermore, the limitations of this research will be discussed (§5.2) and recommendations for future research are provided (§5.3).

In order to provide answers to the research questions regarding this thesis: *'To what extent do the economic data of pharmaceutical companies justify high budget impacts through the exertion of high prices?'* and *'To what extent are net profits reinvested into the development of new drugs?'* a framework was constructed containing multiple variables to be analyzed and compared within a sample and across industries. The results are interpreted below and linked to the thesis questions.

5.1 INTERPRETATION OF THE RESULTS

Period of exclusivity

Perhaps the most striking finding in this research was concerning the period of exclusivity on the market after the drug is launched for sale. According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), by the time a medicinal product reaches the market an average of 12-13 years will have elapsed since the first synthesis of the new active substance (EFPIA, 2016). This would imply that on average, 7-8 years of patent protection is left resulting in exclusive sales without competition. The mean and median findings obtained concerning the drugs in this sample substantially deviate from these figures.

Pharmaceutical companies are constantly attempting to extend the duration of a patent by slightly altering formulations or targeting different population groups (Gupta, 2010). As figure 1 (p.11) in the theoretical framework illustrates, the effect of patent expiration on the revenue of pharmaceutical companies can be substantial. Therefore, from an opposite perspective, one can imagine the effect on the company revenue if 7-8 years of patent protection remaining turns out to be more than 10 years. In fact, out of the 28 drugs in the sample 21 drugs have more than 8 years of patent protection left. It might therefore be questionable whether the pharmaceutical companies in the sample have anticipated on this period of exclusivity remaining after market penetration when determining the price of their drug. The alternative might be that the average 7-8 years of patent protection is simply being used to justify a higher price. The results regarding the period of exclusivity deviate substantially from figures found in the theory and industry. Therefore, one might question whether the presented data regarding exclusivity on the market justify high budget impacts through the exertion of high prices.

Product revenue ratio

The objective of the product revenue ratio analysis was to determine what the impact was of the drug in the sample in comparison with the drug that contributes most to the revenue in a company. In addition, the inclusion of the product revenue ratios would provide a better image of where the drugs in the sample are positioned within the company.

More ideally would be to identify how much profit can be allocated to the drugs in the sample, however there are no companies that report how much expenses are attributed to specific drugs in their portfolio, therefore product revenue ratios provide the most information to be obtained. Moreover, product revenue ratios identify to what extent a company is dependent on a product. The number of products in portfolio has been determined from the year in which the company launched the product in order to obtain a fair view of the potential risk a company endured at launch.

The results illustrate that in the case one of the companies holds a drug with a relatively high impact on the total revenue of that company, it holds a relatively low number of products in portfolio, meaning the company might be more dependent on the launched product. This perhaps has an effect on the risk a company bears when launching a new product on the market and therefore the price determination of a drug. The more products a company holds in its portfolio with patent protection, the less it is dependent on one single product to generate net income, which may spread the risk accompanied with the launch of a new drug. Moreover, holding a number of products in portfolio may lead to a more constant/stable stream of revenue therefore diminishing risk. When linking this to the main research question, one may conclude that there are differences with regard to the level of risk companies endure which in my opinion need to be addressed. Otherwise companies may simply use these arguments to justify a higher price. There is no uniform measure of risk attached to the launch of a new drug with regard to differences in the size of pharmaceutical companies.

Furthermore, 6 out of the 26 drugs in the sample were accountable for the highest product revenue ratio in the company in 2017. Obviously, the EMA approval dates varied from 2006-2017 meaning some drugs have had a longer uptake period resulting in a longer period of sales. Therefore, it is unclear whether more (recently launched) drugs will be added to this list the coming years and can be considered a blockbuster drug for their company.

Clinical risk

The probability of new drugs entering the market increases with the number of products a company holds in phase 3. Increasing numbers in the pipeline generate a platform for future growth. Studies have estimated phase transition success rates and found that the probability of success from phase 3 to New Drug Administration filing is 58.1% (n= 1491) (Thomas, et al., 2016). Therefore, companies that hold a greater number of products in phase 3 have a higher probability of drugs being launched and therefore profits to be generated in the near future. The results illustrated that the number of phase 3 drugs a company holds increases with the global revenue of the company. It is therefore questionable whether a company with more than 30 products in phase 3 bears the same level of clinical risk as a company with 0 products in phase 3 and whether the same pricing strategies are in order.

The justification of a high budget impact through the exertion of a high price may not be in order for all drugs in the sample after evaluating abovementioned variables. Significant differences exist in portfolio size, pipeline, product dependency and period of exclusivity which all contribute to different levels of risk and in the end influences the price determination of a drug.

Financial

In order to discover whether net profits are reinvested into the development of new drugs, it is important to understand how net profits are allocated within a company. Net profits can either be paid out as dividends to shareholders or can be retained in the company for future growth. Only considering the dividend payout ratio however will not be sufficient to judge whether net profits are spent in a way that can be considered socially acceptable.

A first step in evaluating whether the sample profit margin can be considered acceptable is by taking a look at the net profit margin in comparison with other industries. From the results is it is visible that the Software, Medical Equipment and Agricultural industry display a higher median net profit margin than the profit margin in the sample. The Agricultural industry, referring to crops, livestock, fish, and other agricultural services may be the industry that bears the closest resemblance to the pharmaceutical industry. These are both industries where a great amount of capital is required, new technologies keep on emerging to facilitate production and where the safeguarding of public health needs to be guaranteed. As 3 out of 6 industries display a higher median net profit margin, with the

agricultural industry being one of them, this might provide valuable insights regarding the acceptability of profits in this sample and therefore the justification of a high price.

Subsequently, when considering dividend payout ratios, in my opinion the figures obtained should be interpreted with caution. A relatively high dividend payout ratio does not necessarily indicate that less money is spent on R&D. The dividend payout ratio does not provide any information on the R&D expenses of a company. Dividend policy is dependent on several factors such as profitability, the company mission, the size of the company and the age of the company. Therefore, figure 13 (p.33) is in compliance with the study by (Yusof, 2016) as an upward trend is visible with regard to the dividend payout ratio and global revenue of companies in the sample. In general, a starting company with the aim to expand will not pay out as much dividends as an older, more established company that has generated more revenue and more profits. The dividend payout ratio and dividend yield merely provide information on the capital gains returned to shareholders. Therefore, a company should be able to pay out all of its profits and may still be operating in a socially acceptable way as an equal share is being spent on R&D for the development of new drugs. Providing a sufficient return on investment is essential to attract and retain investors and capital for the development of new drugs. How these returns are realized may be different in each company therefore no uniform dividend payout ratio can be considered optimal in my opinion.

As has been briefly discussed in chapter 4, there exist no direct cash flow movement from net profits to what is being spent on R&D, therefore finding a direct relation between these two balance sheet items is challenging. In my opinion, net earnings and R&D expenses should be addressed separately in the analysis as the R&D expenses denote what is being spent on the development of new drugs. Substantial profits may be considered acceptable when in addition a substantial amount of money is spent on the research and development of new drugs. The results regarding the net profit/R&D ratio illustrate that in the sample, roughly an equal amount of money is spent on R&D as is being left as net profits in the company which in my opinion is the closest approach of determining whether net profits are reinvested into the development of new drugs. By linking this to the sub-question, one can conclude that net profits are in fact reinvested into the development of new drugs. However, when taking a closer look at the individual companies, different conclusions may arise.

Remarkable observations were presented by Gilead sciences. Gilead Sciences displayed a median net profit/R&D ratio of 276% indicating that the amount of net profits were almost three times the amount of R&D expenses in the 12-year period. In addition, the median profit margin of Gilead Sciences over the 12-year period was remarkably high which indicates that the company is growing at a fast pace. It is however questionable whether these figures can be considered acceptable as the share of R&D expenses is significantly lower than the share of net profits. This may provide information on the extent of net profits being reinvested into de development of new drugs. Moreover, abovementioned key ratios deviate substantially from the other firms in the sample and Gilead Sciences may therefore be considered an extreme.

Gilead Sciences only started paying out dividends in 2015, therefore most of the profits were retained in the business. As the sub-question regarding this thesis tries to explain whether net profits are reinvested into the development of new drugs, retained profits that have been spent in the 12-year period were analyzed.

The results indicated that from the two companies (Amgen & Gilead Sciences) that spent more money from retained earnings than on R&D, a substantial amount is spent on the repurchasing of outstanding shares. The repurchasing of outstanding shares can be considered a usual investment activity from growing companies. Buying back shares means acquiring that portion of its ownership that was previously distributed among investors to raise equity capital. Return on investment can be granted in the form of dividends, or in the form of capital gains realized by the sale of shares. Share repurchases is a simple way to pay off investors and therefore results in additional yield for the investors.

it is important to take notice of this as this provides a clear image on the importance of R&D relative to investment activities such as the buyback of shares which results in capital gains for investors. The share of net profits being reinvested into the development of new drugs may be lower for these companies as they have decided to grow their business first. This may be in the benefit of society in the future as an expanding company attracts more capital which can be used to target complex and costly diseases. There is unfortunately no way to determine whether these companies will operate in this way. Therefore, the inclusion of sufficient non-financial statements would be beneficial to the transparency of pharmaceutical companies.

By taking a broader look at the sample one may conclude that on average R&D and net profits are of equal proportions. When taking a closer look at individual companies these proportions may differ substantially, although this does not necessarily have to be of negative influence for the development of new drugs in the long term.

Gilead Sciences was also one of the three pharmaceutical companies in the sample that displayed an acquisition/R&D ratio that exceeds 100% indicating that more money has been spent on the acquisition of business in the 12-year period than was invested in R&D. For these companies it seems that net profits are rather invested in other business activities such as acquisition of business than in R&D. It is again questionable how the costs of acquisition of business can exceed the costs of R&D in a 12-year period when the industry claims R&D is responsible for a great amount of risk and expenses in the development process of new drugs. Moreover, the level of risk may significantly change when a company with a potential drug candidate in phase 3 is acquired instead of a molecule being developed from in-house R&D. This phenomenon is occurring more often where smaller biotechnological companies have developed a new molecular entity and are acquired by larger companies. Obviously, the acquisition of a smaller company requires great capital but at the same time implies less pressure is put on in-house R&D which can lead to the shifting of risk and ultimately to the reduction of capital expenses.

Contrary to the theory, there is no evident upward or downward trend visible in average R&D costs per EMA approval in the sample during the 12-year period as figure 18 (p.36) has shown. In fact, the R&D/approval ratio remains rather constant with some minor fluctuations. In my opinion, judging the R&D productivity over a period of time based on this ratio is challenging as the fruits resulting from R&D costs in year T are visible several years later. Moreover, the development period may deviate substantially for different type of drugs such as biological drugs and non-biological drugs. One apparent observation is however that R&D costs are increasing which would imply that EMA approvals need to increase as well for the R&D/approval ratio to remain constant in the sample. As there is no evident upward or downward trend visible in this sample, this may indicate that the R&D productivity may not be declining the way theory suggests.

The remarkable high number of EMA approvals of Novartis resulting in the relatively low average R&D costs per EMA approval might be indicative of the high productivity of this company. It is however unclear whether these EMA approvals are the result of in-house R&D or from the acquisition of business as this would provide an inaccurate representation of the productivity of the R&D department. Novartis displayed an acquisition/R&D ratio of 65.3% indicating that the total R&D costs were nearly twice the total costs of acquisition of business in the 12-year period and can be considered acceptable for a company of that size. In the case of Gilead Sciences however, that presented even lower average R&D costs per approval, the acquisition/R&D ratio exceeds 100%. It is therefore questionable whether the EMA approvals are the results of productive in-house R&D or from the acquisition of business. The level of risk a company endures may significantly diminish if a large number of new drugs are emerging from the acquisition of business instead of intensive and costly in-house R&D and may have serious consequences when determining the price for a drug.

According to the theory and the industry, there is a high level of risk and uncertainty with regard to the R&D costs of a new drug. There is uncertainty around what molecules eventually are being developed into a successful drug and these risk factors contribute to the price determination of a drug. However, looking at table 6 and taking into account two extremes in the sample with regard to R&D and EMA approvals, it might be the case that the level of risk or uncertainty Novartis had to bear was significantly less with the development of 52 new drugs compared to AbbVie with only 4 drugs in the 12-year period. Moreover, the development of 4 biological drugs targeting complex and severe diseases may have higher risks accompanied with them than with the development of rather simple non-biological drugs. The results illustrate that the clinical and financial risks are not the same for all pharmaceutical companies. It is questionable whether pharmaceutical companies acknowledge these differences in risk or whether these companies hide behind these arguments in order to justify a higher price.

In the debate on high budget impacts through the exertion of high prices, R&D expenses are often the most discussed and analyzed topic. In the results section, the differences in the sample with regard to R&D and SG&A became evident compared to the industry figures provided by the NYU Stern School of Business. As the sample mostly consists of top pharmaceutical companies with respect to revenue, one might conclude that these companies, due to their magnitude, have higher SG&A expenses relative to R&D expenses. Large pharmaceutical companies have more employees, more selling expenses due to more products in portfolio therefore higher SG&A expenses compared to smaller pharmaceutical companies makes sense. It is however questionable whether we expect to see the same growth in R&D as with SG&A expenses for these top pharmaceutical companies. Furthermore, can be wondered what share of the SG&A expenses are attributed to advertising/marketing purposes. The SG&A expenses are not always further specified and even so does not provide enough transparency of the total marketing expenses made.

This research will not go into greater detail with respect to accounting principles as this mainly comprehends a qualitative study. It would however be interesting to see these results being developed from an accounting perspective as well, therefore further research should be done.

Fair medicine

Perhaps there should be an alternative way to develop innovative drugs that is more transparent and may lead to the exertion of lower prices. The current business model for developing innovative drugs is solely dependent on the financing of pharmaceutical companies. Therefore, the pharmaceutical companies bear all the risk that are accompanied with the research and development of innovative drugs. Moreover, pharmaceutical companies are shareholder driven which means it is rational that investors expect to see the biggest return possible on their investment. With the current business model, the conflict of interest between multiple parties comes to light as both profit maximization as well as achieving lower drug prices is not possible.

'Fair Medicine' is an initiative founded by prof. dr. Hans Büller and dr. Frans de Loos in the objective to realize fair drug prices by establishing a new business model. Fair medicine brings together a coalition of multiple stakeholders such as patient associations, hospitals, researchers, social investors and pharmaceutical companies to invest in the R&D and therefore share the risk accompanied with the development of a new drug. In the suggested model, acceptable profit margins are agreed upon prior to development. All parties share proportionally in the profit and can expect a socially acceptable return on investment. In addition, the drug that is being developed is not allowed to be sold to other

companies in order to prevent additional margins being added to the eventual price of the drug. It is also not possible to sell your share in the coalition during the development process as this is one of the factors that drives up the price of a drug. Above all, transparency is expected to be one of the main principles regarding this model. On paper, this model seems to have eliminated all factors that may negatively affect the price of a drug. The ministry of VWS has granted Fair Medicine a subsidy of 2.9 million euro's in 2016. The near future should clarify whether this proposed business model works in reality as the first product resulting from this business model will be tested on volunteers in 2018. (Fair Medicine, 2018)

5.2 RESEARCH LIMITATIONS

Effective research of this study took place over a period of approximately 20 weeks. This restriction in time and resources has inevitably led to a few choices, which may have had an influence on the quality of this research.

Although multiple previous studies have tried to explain what factors in general account for the claim of a high drug price, little is known on the assessment of presentable data of multiple pharmaceutical companies and whether these claims can be considered valid. Therefore, as has been discussed, a framework was constructed containing multiple variables to be analyzed and compared as no such framework previously exists. All variables were included through an iterative process of literature and annual reports review. There could have been variables that were not included in the framework but could add significant value to this research. Even though initially data was collected together among the three researchers to ensure consistency in the way of data collection, there could have been minor differences in interpretation during the collection of data.

The researcher is the research instrument in qualitative research. It is therefore important to be critical of my own influence in this research. I did use research triangulation for the analysis as did the other researchers of this study as the initial part of data collection was conducted together. Therefore, the analysis might have been less affected by my own influences. However, during the individual parts regarding the sub-questions of this thesis, this was not the case.

The timeframe chosen for the analysis of company data was from 2006-2017 as this would date back to the first drug included in the sample. It would however provide more detail if a longer period was chosen to acquire a better image of the situation before product launch as well as after the launch. This was not possible because not all data regarding companies in the sample could be collected for that period in time. This also explains the exclusion of the two companies prior to 2006. In addition, the analysis of a substantial period after product launch is in my opinion necessary to determine the financial effects of the drug in the company during the entire period of exclusivity. This was not possible as most of the drugs in the sample were launched relatively recently.

Industry level data was available for the period 2006-2015 resulting in a shorter period of analysis for the industry level data compared to the sample data. Therefore, the results obtained regarding the industry level data are valid but might present an underestimated image.

In the presence of more time, more generic companies could have been included in the analysis. It is however important to only include pure generic companies therefore the currently included companies do provide a representative image of the generic industry in my opinion and therefore provide valid results.

It would provide valuable insights to discuss the most striking findings in the framework with representatives of the pharmaceutical companies and perhaps government institutions. It would

however be questionable whether the offices of pharmaceutical companies in the Netherlands would be able to provide answers as the headquarters are situated in other countries where regularly the annual reports are drafted.

Even though all data has been analyzed with statistical software Stata, no additional statistical tests have been performed in the light of this study being a qualitative study with financials as support.

5.3 RECOMMENDATIONS FOR FUTURE RESEARCH

This study merely focused on the availability and presentation of economic data of pharmaceutical companies and whether these may justify high budget impacts through the exertion of high prices.

For future research I would recommend improving the framework that was constructed by critically evaluating what additional variables may provide a significant contribution. Furthermore, I expect there to be valuable insights when a detailed case study will be conducted for each pharmaceutical company as well as each individual product with a high budget impact. This will however take a considerable amount of time and will go beyond solely researching the transparency of pharmaceutical companies.

In the desired setup, next to evaluating the available information presented by the companies, it would add value to include an accounting perspective on this matter in which the financial data are further analyzed. After results have been obtained, I would recommend interviewing relevant stakeholders as well as executives from the pharmaceutical companies who can adequately comment on the obtained results.

In Appendix D (p.62), a list of potential interview questions has been drawn up.

6. CONCLUSION

The continued rise in drug prices leading to high budget impacts is an important issue in many countries, the Netherlands being no different. Although multiple previous studies have tried to explain what factors in general account for the claim of a high drug price, little is known on the assessment of presentable data by multiple pharmaceutical companies and whether their claims for a high drug price can be considered valid. This research report designed a framework containing multiple variables which can be used to establish patterns and evaluate claims presented by the industry. An iterative process of annual reports review has led to the establishment of this framework and is used in answering the research questions of this report. The sub-question of this research report is as follows: *To what extent are net profits reinvested into the development of new drugs?*

There exists no direct cash flow movement from net profits to what is being spent on R&D. Therefore, finding a direct correlation between net profits and R&D is merely possible through company statements made public. However, the lack of sufficient non-financial information in annual reports relating to retained profits, shareholder payouts and R&D expenses make it questionable whether there exists a certain policy regarding R&D reinvestments and the presence of a correlation between profits and R&D expenses.

The net profit/R&D ratio may be the closest approach of determining whether net profits are reinvested into the development of new drugs and indicate that in this sample roughly an equal amount of money is spent on R&D as is being left as net profits in the company. Although substantial differences exist when taking a closer look at individual firms, this does not necessarily have to be of negative influence for the development of new drugs in the long term. The inclusion of sufficient non-financial statements would be beneficial to the transparency of pharmaceutical companies and would help to understand the divergent differences that exist between the pharmaceutical companies.

These differences exist in almost all variables that have been used in this framework most prominently in the period of exclusivity of the drugs on the market. The results regarding the period of exclusivity deviate substantially from figures found in the theory and industry. Therefore, one might question whether the presented data regarding exclusivity on the market adds to the justification of high budget impacts through the exertion of high prices.

The justification of a high budget impact through the exertion of a high price may not be in order for all drugs in the sample. Significant differences exist in portfolio size, pipeline, product dependency and period of exclusivity which all contribute to different levels of risk companies bear. These differences need to be addressed otherwise companies may simply hide behind general risk factors to justify a higher price.

One apparent observation in this study showed that R&D costs are in fact increasing during the 12-year period such as theory suggests. The R&D productivity may however not be declining in the way theory suggests as there is no evident upward or downward trend visible in this sample with regard to R&D costs/EMA approval during the 12-year period. Judging the R&D productivity should be done with caution however as significant differences may exist between type of approvals (innovator drugs) and development phases resulting in divergent periods of analysis with regard to productivity. The results illustrate that the clinical and financial risks are not the same for all pharmaceutical companies. It is questionable whether pharmaceutical companies acknowledge these differences in risk when determining the price of a drug.

Even though there is homogeneity in the sample as the study population only concerns drugs with a high financial risk, substantial differences have been illustrated between the individual firms. Therefore, individual firms should not be able to hide behind the general known risks of this industry that may only apply for smaller, more innovative firms.

Considering the points of discussion and the room for improvement identified in this report, this framework can be best used as a template for further optimizing the assessment of economic data presented by pharmaceutical companies. No unambiguous conclusion can be drawn from the assessment of this framework with regard to the justification of high prices explained by the economic data of pharmaceutical companies. Even though sample results are well within industry averages, extreme observations are presented when considering individual companies. The presented results do provide a basis on which to further investigate, from different perspectives, and contribute to a better understanding of what factors may be of influence in determining the price of an innovator drug.

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Table 2. Study population

Company name	Trade name drug	Year	Fin. Arr.	Generic	Lock	Orphan	Excluded
1. **Abbvie**	Exviera	2015	√				
	Viekirax	2015	√				
2. **Aegerion**[2]	Lojuxta	2013	√				
3. **Alexion**	Soliris	2007	√			√	
4. **Amgen**	Repatha	2015	√				
5. **Bayer**	Xarelto	2008	√				
6. **Biogen**	Spinraza	2017			√		
7. **Bristol-Myers Squibb**	Eliquis[3]	2011	√				
	Daklinza	2014	√				
	Opdivo	2015	√		√		
8. **Boehringer Ingelheim**	Pradaxa	2008	√				
	Ofev	2015	√			√	
9. **Daiichi Sankyo**	Lixiana	2015	√				
10. **Genzyme**[4]	Fabrazyme	2001	√			√	√
	Myozyme	2006	√			√	
11. **Gilead**	Sovaldi	2014	√				
	Harvoni	2014	√				
	Epclusa	2016	√				
12. **Intermune**[5]	Esbriet	2011	√			√	

[2] Acquired by Novelion
[3] In collaboration with Pfizer
[4] Acquired by Sanofi
[5] Acquired by Roche

Company name	Trade name drug	Year	Fin. Arr.	Generic	Lock	Orphan	Excluded
13. Johnson & Johnson	Zytiga	2011	√				
14. Merck & Co	Keytruda	2015	√		√		
	Zepatier	2016	√				
15. Mylan				√			
16. Novartis	Jakavi	2012	√			√	
17. Otsuka	Jinarc	2015	√			√	
18. Pfizer	Ibrance	2016	√		√		
19. Roche	Perjeta	2013	√				
20. Sanofi	Praluent	2015	√				
21. Sun Pharmaceuticals				√			
22. Teva				√			
23. Transkaryotic Therapies	Replagal	2001	√			√	√
24. Vertex	Orkambi	2015	√				
	Kalydeco	2012	√			√	

Business strategy: Most annual reports start with an executive summary, including *key financial figures, a business overview* and *strategic objectives*. For this purpose, an illustration of (changes in) the companies' business, business results, strategic objectives. For a detailed discussion, standing out observations and company specific results are highlighted by some companies.

R&D / pipeline statements: This topic includes a discussion of the R&D process in the industry in general and/or a detailed discussion of the R&D /pipeline strategy that the company maintains. Also, companies might elaborate on disease specific focus areas or different phases in the R&D process. Furthermore, it is possible that a definition is presented for cost items that are considered an R&D expense.

R&D expenses: This item includes a disaggregation of the Research and Development expenses that occurred in the relevant fiscal year. The level of disaggregation is considered. For a detailed disaggregation, at least three separate cost items needed to be presented. Difference with the prior topic (*R&D / pipeline statements*) is that this topic is solely focused on financial figures.

SG&A expenses: This item includes a disaggregation of the Selling, General and Administrative expenses that occurred in the relevant fiscal year. The level of disaggregation is considered. For a detailed disaggregation, at least three separate cost items needed to be presented.

Risks: This topic includes a discussion of risks concerning the business of the pharmaceutical company. Financial risk, such as credit risk and currency risk, are excluded. This topic can include risks for the pharmaceutical industry in general, but also risks that are only applicable to the specific company and/or specific products. This topic often includes risk of generic competition, third party collaborations, short earning-back periods and discontinuation of certain products.

Subsidiaries: This item pertains an overview of all subsidiaries of the company.

Acquisitions: This reporting item concerns the acquisitions of businesses by the company under review. This includes, but is not limited to, the names of the companies, acquisitions cost, acquired intellectual property research & development (IPR&D), goodwill and agreed terms.

Current drug portfolio: This item concerns an overview of all pharmaceutical products that the company currently markets. Some companies might limit this overview to an overview of key products or products under patent protection. This overview can include brand names, API's, indications and product revenues.

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[6] R&D/pipeline statements, R&D expenses & Profit policy are covered in this research report

Current pipeline portfolio: This item includes an overview of the company pipeline. This overview can include all pipeline products or only late-stage products. This can be accompanied by a description of indications, API's, current development phase and expected revenues.

Intellectual property statements: This topic concerns a discussion of the issue of intellectual property and/or patenting. It may include a general discussion of the patenting process but can be extended to a detailed discussion in relation to company specific R&D processes.

Patent overview: This item pertains an overview of expected patent expiry dates. This discussion may include secondary patents or market exclusivities, such as pediatric indications and orphan designations.

Social impact: This topic concerns a discussion of the relation between the company and social welfare. It is limited to three items: drug pricing, reimbursement/regulations and health outcomes. A discussion of this topic can include a presentation of the companies' impact on these abovementioned issues or a reflection on how the company is affected by either of the topics.

Profit policy: This item concerns the profits of the company. It includes a discussion of (changes in) the net income and how profits are relocated in the business. Some companies pay out dividends and might motivate any changes in paid out dividends. Some companies reinvest their earnings and might discuss how profits were put to use. A motivation for either choice might also be included in the discussion.

Table 4. Period of exclusivity of the drugs in the sample

Company name	Trade name drug	Patent Expiry	EMA Market Approval	Period of Exclusivity (years)
Genzyme	Myozyme	2021	2006	15
Alexion	Soliris	2021	2007	14
Boehringer Ingelheim	Pradaxa	2021	2008	13
	Ofev	2020	2015	5
Bayer	Xarelto	2020	2008	12
InterMune	Esbriet	2026	2011	15
BMS	Eliquis[7]	2023	2011	12
	Daklinza	2027	2014	13
	Opdivo	2030	2015	15
Janssen Cilag	Zytiga	2016	2011	5
Vertex	Kalydeco	2025	2012	13
Novartis	Jakavi	2026	2012	14
Roche	Perjeta	2020	2013	7
Aegerion	Lojuxta	2016	2013	3
Gilead	Sovaldi	2028	2014	14
	Harvoni	2030	2014	16
	Epclusa	2028	2016	12
AbbVie	Exviera_Viekirax	2029	2015	14
	Viekirax	2029	2015	14
Otsuka	Jinarc	2020	2015	5
Daiichi Sankyo	Lixiana	2023	2015	8
Amgen	Repatha	2029	2015	14
Merck & Co	Keytruda	2028	2015	13
	Zepatier	2030	2016	14
Sanofi Aventis	Praluent	2029	2015	14
Vertex	Orkambi	2026	2015	11
Pfizer	Ibrance	2023	2016	7
Biogen	Spinraza	2027	2017	10

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[7] In collaboration with Pfizer

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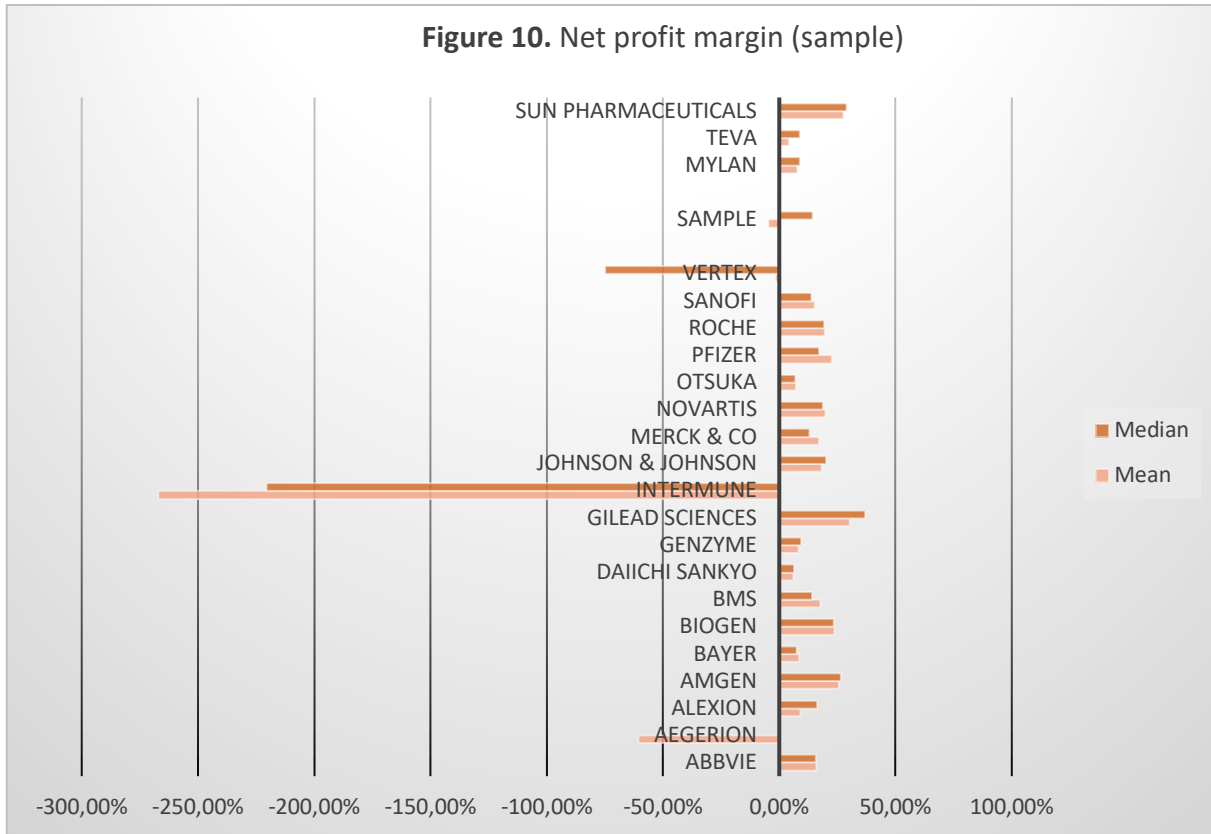
Figure 10. Net profit margin (sample)

Figure 11. Net profit margin
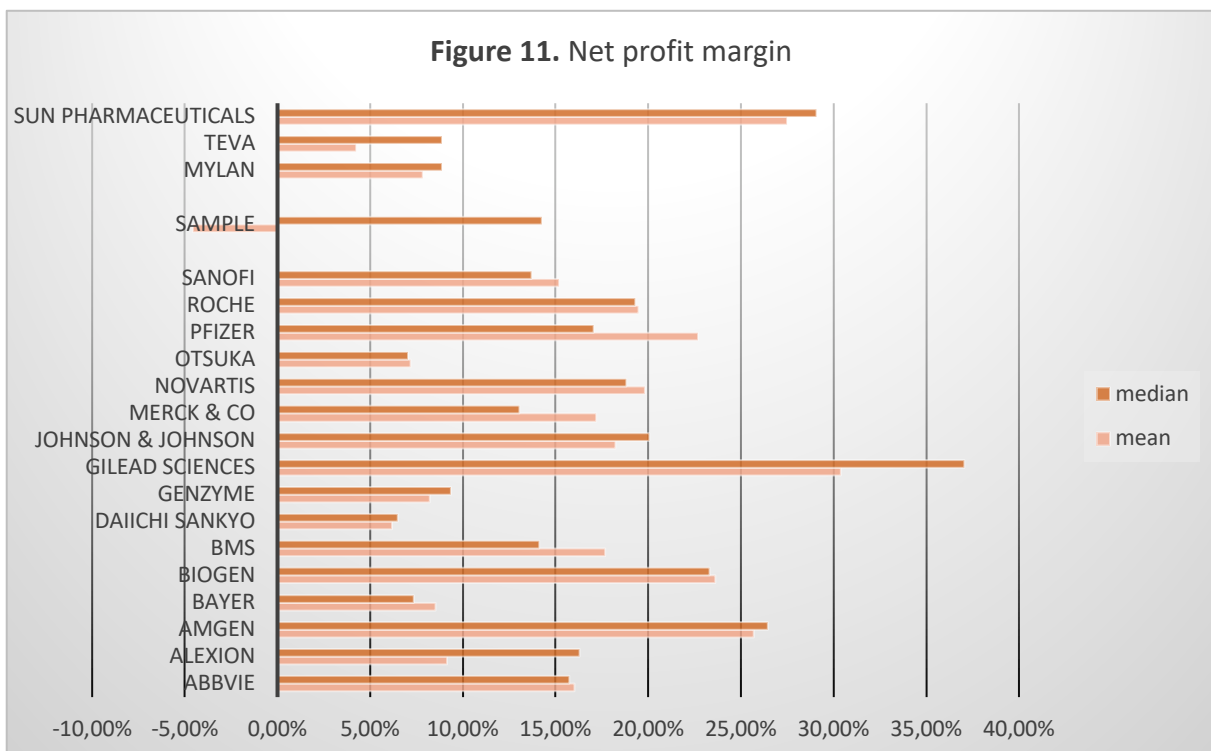
Figure 11 shows the net profit margin for all companies in the study population that displayed a positive median/mean net profit margin. This has led to the exclusion of 3 firms (Aegerion, Intermune & Vertex) in this figure.

Figure 15. Dividend yield (in %)

Figure 15. Dividend yield (in %)

AERO	CHIPS	SOFTW	HARDW	SAMPLE	MEDEQ	AGRIC
1,70	2,14	1,61	1,80	2,38	1,12	1,48

median

Table 8. Acquisition/Third party relations

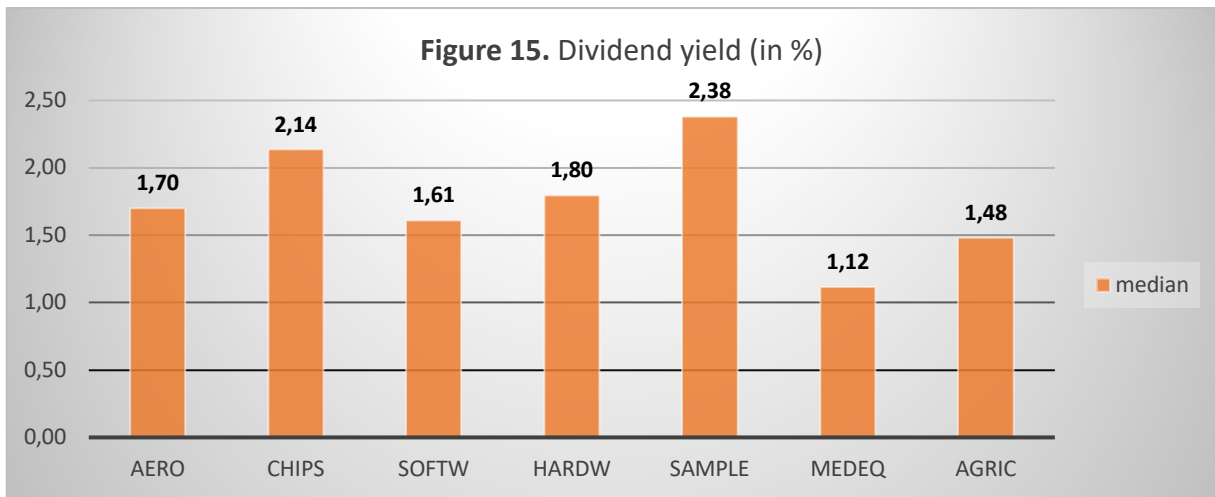| Company name	Trade name drug	Early stage acquisition		Third party dependency	
		Price (in millions of US $)	*Phase*	*Company relation*	*Type of collaboration*
Genzyme	Myozyme	-	-	-	-
Alexion	Soliris	-	-	-	-
Boehringer Ingelheim	Pradaxa	-	-	-	-
	Ofev	-	-	-	-
Bayer	Xarelto	-	-	Janssen R&D	Co-development
InterMune	Esbriet	-	-	-	-
BMS	Eliquis[8]	-	-	Pfizer	Co-development
	Daklinza	-	-	-	-
	Opdivo	2400	1	Medarex	Co-development
Janssen Cilag	Zytiga	-	-	British Tech Group	License
Vertex	Kalydeco	-	-	-	-
Novartis	Jakavi	150	3	Incyte	Licensing US
Roche	Perjeta	46800[9]	3	-	-
Aegerion	Lojuxta	0[10]	4	Amryt Pharma	Licensing EU
Gilead	Sovaldi	11200[11]	2.5	-	-
	Harvoni	-	-	-	-
	Epclusa	-	-	-	-
AbbVie	Exviera_Viekirax	-	-	-	-
	Viekirax	-	-	-	-
Otsuka	Jinarc	-	-	-	-
Daiichi Sankyo	Lixiana	-	-	-	-
Amgen	Repatha	-	-	-	-
Merck & Co	Keytruda	41100[12]	-	-	-
	Zepatier	-	-	-	-
Sanofi Aventis	Praluent	-	-	Regeneron	Co-development
Vertex	Orkambi	-	-	-	-
Pfizer	Ibrance	90000[13]	0	-	-
Biogen	Spinraza	-	-	Ionis	Co-development & Commercialization

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[8] In collaboration with Pfizer

[9] Acquisition of remaining 44% of interest in Genentech (originator)

[10] Merger with Novelion

[11] Acquisition of Pharmasset (originator)

[12] Acquisition of Schering-Plough who acquired Organon (originator)

[13] Acquisition of Warner-Lambert (originator)

Erasmus University Rotterdam

List of potential interview questions

<u>Reporting</u>

♦ Generally, the Board of Directors determine whether dividend policy changes. What specific factors contribute to changes implemented by the Board of Directors in your company regarding dividend policy?

If necessary, elaborate on

- ✓ *Specific annual factors*
- ✓ *Expectations of shareholders*
- ✓ *The consequences resulting from these implemented changes on the company equity*

♦ Does dividend policy in any way affect the decisions made regarding R&D expenses, and if so in what way?

♦ Differences in reporting were found in the annual reports of Otsuka and Daiichi Sankyo regarding R&D statements as they focused more on KPI's and less on the development process and regulations. These two companies were the only two Asian (both Japanese) companies in this sample and mostly operate in Japan. Could these differences in reporting be the results of geographical differences with respect to expectations of their shareholders?

If necessary, elaborate

- ✓ *Do you believe your approach provides more transparency on the development process and why?*

♦ What determines how detailed R&D expenses are displayed in your annual report?

If necessary, elaborate

- ✓ *A disaggregated view of the expenses would provide more transparency in my opinion, do you agree? And what would be reasons for not doing so?*

♦ Are salaries of R&D personnel included in the R&D expenses presented in the annual reports?

If necessary, elaborate

- ✓ *If so, wouldn't that provide a distorted, perhaps overestimated representation of research and development expenses in the case only aggregated expenses are presented?*

◆ What is your view as representative of your company on the public debate on rising drug prices and unaffordable care?

Variables

◆ In what way does the period of exclusivity remaining after market penetration play a role in determining the price of a drug in your company?
If necessary, elaborate

   ✓ *How flexible are patent expiry dates?*

   ✓ *Is there a possibility of patent extension and what effect would this have on sales and the price of the drug?*

◆ To what extent do products in the pipeline, specifically in late phases, affect the clinical risks that are mentioned in the annual reports? Are these (levels of) risks displayed in the price of a drug and if so, has that been made noticeable in any company filings/statements?
If necessary, elaborate

   ✓ *Do you agree that smaller companies with less products in the pipeline, therefore less expected revenue, do not endure the same risk when launching a new drug? If not, why?*

   ✓ *Would it be fair to expect a difference in the price determination of drugs with respect to different levels of risk?*

◆ To what extent does portfolio size influence the risk accompanied with the launch of a new drug and would this be noticeable in the price of a drug?
If necessary, elaborate

   ✓ *How does dependency on one single drug influence the price of a drug?*

Financial

♦ What direct or indirect relation exists between net profits that are retained in the business and R&D expenses?

♦ To what extent are the costs of failed projects incorporated into the eventual price of a newly launched drug in your company?

♦ What correlation exists between dividend policy and firm's size with respect to revenue?

♦ For what reasons may the repurchasing of own shares prevail R&D expenditures in your company?

If necessary, elaborate

  ✓ *To what extent is this beneficial to society or is it mostly beneficial to shareholders?*

♦ How come acquisition of business expenses exceed R&D expenses in your company and to what extent does this result in increased value/additional drugs?

If necessary, elaborate

  ✓ *Does this in any way affect the risk accompanied with the launch of a new drug?*

  ✓ *If so, has there been accounted for this change in risk in the determination of the drug price?*

  ✓ *Do you think this is a healthy business strategy, please elaborate?*

♦ What are the plans of your company to improve R&D productivity in the coming 5 to 10 years?

♦ To what extent are marketing costs incorporated in the total SG&A expenses or other balance sheet items?

If necessary, elaborate on

  ✓ *The ratio SG&A expenses and R&D expenses*