R&D productivity and disruptive innovation

An empirical analysis of the emerging biotechnology sector

Master Thesis

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Preface

Dear reader,

For most of the last six years, I learned how biological systems can be studied and harnessed to make all kinds of societally beneficial products, such as medicines. Therefore, it has been a pleasure to dedicate my master thesis to a topic that allowed me to learn about the many different aspects of drug innovation systems and the management of a drug-developing firm. It has been particularly intellectually stimulating to read and think about economic reasons why promising radically new biotechnologies may or may not have had the desired impact. While being amidst a pandemic, it has been enthralling to see that one of the latest biotechnological advances - the mRNA vaccine - is saving many lives. This observation has been a source of inspiration. It reminded me of how important it is to safeguard our drug innovation system and ensure that medicines are accessible for as many people as possible.

I would like to express my sincere gratitude to Prof. Cees van Beers for supporting and mentoring me throughout my thesis process. I am grateful for the opportunity to study this topic and for the helpful guidance in shaping and conducting my research. I would also like to thank Prof. Ibo van de Poel for sharing his interesting views, valuable suggestions and our fruitful discussions. Furthermore, I would like to thank Prof. Marc Fischer and my brother, Jelmer, for their support in my efforts in estimating cumulative drug sales. Finally, I would like to thank all my friends and family for their support in the past months.

Eline Doornenbal
Leiden, July 2021

Executive summary

The R&D productivity crisis is among the most pressing issues in the drug industry. The increasing costs and stable R&D outputs jeopardise the industry's economic health, drug innovation, and the accessibility and affordability of medicines. The pharmaceutical R&D productivity problem is expected to be diminished due to biotechnological breakthroughs and the emergence of biotechnology firms. As a result, significant public and private investments and policy measures are aimed at stimulating the development of the biotechnology sector. In addition, firms in the pharmaceutical industry are adopting organisational strategies to mimic biotechnology companies. However, based on previous studies, the measures to stimulate the development of the biotechnology sector are not justified. Empirical evidence on the impact of the biotechnology revolution on pharmaceutical R&D productivity is limited and contradicting. Therefore, it is important for improving pharmaceutical R&D productivity to grasp biotechnology firms' current and future contributions to R&D productivity. The research question in this thesis is as follows:

To what extent can disruption of the pharmaceutical industry by biotechnology firms reduce its R&D productivity decline?

To answer the research question, first, I assessed the current contribution of biotechnology firms to pharmaceutical R&D productivity. For every drug approved by the FDA between 2008 and 2015, I quantitatively analysed the relationship between biotechnological organisational characteristics and three determinants of R&D productivity: the commercial success, innovativeness and medical importance of the new drug. Second, I addressed the research question by examining whether biotechnology firms disrupt the pharmaceuticals market via new-market disruption. I empirically tested for the presence of elements of the concept of new-market disruption using statistical tests.

It is concluded that disruption by biotechnology firms does not and will not reduce the pharmaceutical R&D productivity decline. Instead, the development of new biotechnology firms likely has an adverse impact on R&D productivity. Moreover, new-market disruption in the drug industry is improbable to occur and will not provide the drastic reform the pharmaceutical industry needs to improve its R&D productivity.

It is argued that the current contribution of biotechnology firms is not beneficial for R&D productivity because none of the defining organisational characteristics of a biotechnology firm relates to commercial success. Moreover, biotechnology firms likely have better odds at developing innovative and medically-important medicines, but this comparative advantage is attributed to extrinsic rather than intrinsic factors.

To improve their commercial capabilities, it is recommended for biotechnology firms to gain more commercial experience, to improve their knowledge breadth for the recognition of commercial opportunities and to reap economies of scope. Venture philanthropists can play a key role for enhancing biotechnology firms' commercial capabilities by providing access to long-term capital investments, intimate partnerships and a network of diverse knowledge. For pharmaceutical firms, it is recommended to continue to invest in a broad R&D project portfolio to reap economies of scope in research and commercialisation. In contrast to common strategic advice, this study found no comparative advantage for biotechnology firms to focus on drug discovery and development and for pharmaceutical firms to focus on downstream activities, such as marketing and manufacturing.

Examples of extrinsic factors explaining biotechnology firms' innovative edge are the close relationship with academia, their function of filling in the translational research gap and the financial attractiveness for university scientists to establish a new firm to monetise their intellectual property. Therefore, it is recommended for biotechnology executives to nurture their bonds with universities, research institutes and hospitals. Pharmaceutical firms can also reap benefits from the extrinsic factors. Therefore, for pharmaceutical firms, it is advised to establish close partnerships with academia, invest in translational research and improve financial rewards for university scientists for their intellectual property.

It is argued that, due to industry-specific aspects, new-market disruption of the pharmaceutical industry by biotechnology firms is improbable to occur and cannot provide the drastic reform the pharmaceutical industry needs to improve its R&D productivity. Pharmaceutical incumbents generally have a comparatively high level of sustained revenues and much time, allowing for a sufficient and timely response to technological change that new biotechnology firms bring about. Hence, it is recommended that executives of drug-developing firms be cautious about adopting strategies derived from disruptive innovation theory. These strategies are unlikely to have the desired effect because mechanisms of new-market disruption do not play a prominent role in the drug industry. In addition, strategies derived from disruptive innovation theory are competitive and fall short of significant opportunities that arise from collaboration in the drug industry. Due to co-opetitive inter-organisational dynamics in the pharmaceutical industry, it is recommended for drug-developing firms to adopt strategies derived from co-opetition instead.

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List of abbreviations

CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
FDA	Food and Drug Administration
NBE	new biological entity
NCE	new chemical entity
NDA	new drug application
NME	new molecular entity
M&A	mergers and acquisitions
OLS	ordinary least squares
R&D	research and development

Chapter 1

Introduction

This chapter introduces the problem under investigation in this thesis. Moreover, it addresses how this problem is practically and scientifically relevant. Furthermore, this introductory chapter states the research objective and presents the research questions and hypotheses. The chapter concludes with the thesis approach and structure.

1.1 Problem definition

1.1.1 Background

The research and development (R&D) productivity[1] decline of the pharmaceutical industry[2] is a significant threat to the industry's profitability and viability (Munos, 2009). The problem of the pharmaceutical R&D productivity is that input - the R&D costs - is increasing while the output - newly discovered and approved drugs[3] - is stable. The trend of declining R&D productivity has prevailed for over six decades now, despite significant technological advancements and attempts to solve the problem. Between 1950 and 2008, the number of approved drugs annually remained stable, while the R&D costs per new drug increased exponentially by 13.4% per year (Munos, 2009). The productivity decline became particularly urgent due to two matters: (1) an increasing number of drugs approaching their patent expiration date and (2) an insufficient number of promising drug candidates to recoup the increasing R&D investments (Paul et al., 2010). When a commercially-successful drug cannot be replaced after patent expiration, the patent expiration leads to a sharp decrease in sales due to price competition, referred to as a "patent cliff". Patent cliffs are increasingly occurring, which

[1] R&D productivity is defined as the ratio of the R&D input and output.

[2] The terms "pharmaceutical industry" and "drug industry" are used interchangeably in this thesis to refer to the collective of actors and institutions involved in the development and commercialisation of medicines.

[3] The terms "drugs" and "medicines" are used interchangeably in this thesis to refer to any substance for preventing, curing or relieving symptoms of a disease.

poses an urgent threat to the industry's economic health.

The pharmaceutical R&D productivity decline is expected to reduce due to the technological advancements resulting from the emerging biotechnology sector.[4] The emergence of the biotechnology sector, starting from the late 1970s, transformed the pharmaceutical industry drastically. From the earliest foundation of modern drug discovery in the 1870s to the emergence of the first biotechnology firms in the 1970s, drug-developing firms performed an insignificant amount of R&D activities (Pisano, 2006b). New-drug development was a chemistry-based trial-and-error process. The biological knowledge and analytical tools to discover and develop new drugs and drug targets were minimal. A limited number of large pharmaceutical companies dominated the industry and large barriers prevented new firms from entering. From the mid-twentieth century onwards, modern drug discovery has experienced revolutionary scientific and technological breakthroughs. Together with the new availability of funds from alliances and private and public equity, these breakthroughs have resulted in the emergence of thousands of new small biotechnology firms. This "biotech revolution" has led to the widespread expectation that the biotechnological advancements would translate to significant improvements in drug discovery and development (Nightingale & Martin, 2004). Therefore, the emergence of the biotechnology sector is expected to improve pharmaceutical R&D productivity, referred to as the "promise of biotech".

1.1.2 Practical relevance

Research on the impact of biotechnology firms on pharmaceutical R&D productivity can indicate directions in which corporate strategies, investments, and policy should go to reduce the R&D productivity decline. Improving pharmaceutical R&D productivity is crucial for making medicines affordable and accessible. Based on the "promise of biotech", investors and policymakers have been investing heavily in the development of the biotechnology sector (Hopkins et al., 2007). Moreover, pharmaceutical firms have been adopting organisational strategies to become more "biotech-like" (Malerba & Orsenigo, 2015). However, since the R&D productivity has not improved yet, the potential of the biotechnology sector to enhance R&D productivity is questioned (Malerba & Orsenigo, 2015; Hopkins et al., 2007; Pisano, 2006b). As a result, the effectiveness of the investments, policies and corporate strategies inspired by the expected success of biotechnology firms is under debate. Current empirical studies addressing the impact of biotechnology firms on R&D productivity are limited, flawed and contradicting (Drakeman, 2014; Kneller, 2005b, 2005a, 2010; Pisano, 2006b, 2006a; Nightingale & Martin, 2004; Pammolli et al., 2011, 2020; Arora et al., 2009). Therefore, based on current literature, no firm conclusions can be drawn on whether efforts to stimulate further development or imitate the biotechnology sector will increase R&D productivity. This study

[4]The term "biotechnology" in this thesis specifically refers to the branch of biotechnology that relates to healthcare, also called "red biotechnology".

represents the first statistical comparative analysis of biotechnology and pharmaceutical firms regarding their effect on R&D productivity.

1.1.3 Scientific relevance

Current studies on the impact of biotechnology firms on drug discovery and development are predominantly empirical. Therefore, the provision of a theoretical framework can offer a new means for interpreting empirical results on the impact of biotechnology firms on pharmaceutical R&D productivity. This study aims to complement the current body of empirical knowledge by applying Clayton Christensen's theory of disruptive innovation (Christensen, 1997). Disruptive innovation theory is one of the most influential business theories of the last decades. *"Disruption describes a process whereby a company with fewer resources can successfully challenge established incumbent businesses. Specifically, as incumbents focus on improving their products and services for their most demanding (and usually most profitable) customers, they exceed the needs of some segments and ignore the needs of others. Entrants that prove disruptive begin by successfully targeting those overlooked segments, gaining a foothold by delivering more suitable functionality — frequently at a lower price. Incumbents chasing higher profitability in more-demanding segments tend not to respond vigorously. Entrants then move upmarket, delivering the performance that incumbents' mainstream customers require while preserving the advantages that drove their early success. When mainstream customers start adopting the entrants' offerings in volume, disruption has occurred."* (Christensen et al., 2015).

The application of the theory of disruptive innovation to the case of the emerging biotechnology sector tests the theory's generalisability and predictive capacity in a new context. The theory of disruptive innovation has been applied extensively to the case of the healthcare industry in general (Christensen et al., 2000, 2008). However, scholars previously applied the theory to the dynamics between biotechnological entrants and pharmaceutical incumbents in a minimal number of instances and to a limited extent (Kapoor & Klueter, 2014; Birkinshaw et al., 2018). Therefore, this study forms the first thorough application of the theory of disruptive innovation to the emerging biotechnology sector in the pharmaceutical industry.

More generally, the performance of biotechnology firms in the pharmaceutical industry forms a scientifically relevant case study for the investigation of management challenges accompanying the new class of science-based enterprises (Pisano, 2006a). A "science-based business" can be described as *"a commercial enterprise or collection of enterprises that attempt to both create science and to capture value from it"* (Pisano, 2006a). According to Pisano (2006a): *"The vast majority of our stock of business knowledge [...] flows from experience accumulated in very different technological contexts. The management challenges of the science-based business are novel and as such cannot be addressed with indiscriminate borrowing of practices, models,*

approaches, and arrangements that have worked well in other industries, including high-tech industries." A case study investigating challenges in modern drug innovation contributes to the relatively poor body of knowledge on managing science-based businesses (Pisano, 2010). Consequently, insights from this study have the potential to be generalised from medical biotechnology to a broader field of science-based businesses, including nanotechnology and energy.

1.2 Research objective

This study endeavours to increase our understanding of factors that stimulate drug discovery and development. Particularly, it aims to examine to what extent biotechnology firms reduce the decline in R&D productivity - now and in the future. This thesis investigates the current contribution of biotechnology firms to pharmaceutical R&D productivity by linking organisational characteristics to determinants of R&D productivity. Moreover, it examines the future impact of biotechnology firms on R&D productivity by applying the theory of disruptive innovation. By analysing to what extent biotechnology firms can improve R&D productivity, this study aims to assess the effectiveness of current measures stimulating the establishment of or mimicking biotechnology firms. Furthermore, it aspires to complement the current body of empirical studies on the impact of biotechnology firms on R&D productivity with a theoretical basis. Finally, it has the objective to test the applicability of the theory of disruptive innovation in the context of the emerging biotechnology sector.

1.3 Research questions

This study will investigate to what extent disruptive innovation by biotechnology firms can reduce the pharmaceutical R&D productivity decline. Hence, the main research question under investigation is:

To what extent can disruption of the pharmaceutical industry by biotechnology firms reduce its R&D productivity decline?

This thesis will address the main research question by investigating biotechnology firms' current and future contributions to pharmaceutical R&D productivity. First, it will assess the current impact of biotechnology firms on pharmaceutical R&D productivity by addressing the following question:

1. ***What is the contribution of biotechnology firms to pharmaceutical R&D productivity?***

To answer subquestion 1, this thesis will analyse to what extent biotechnological organisational characteristics correspond to relatively high performance in R&D productivity. Assessments

of pharmaceutical R&D productivity consider multiple determinants of R&D productivity: the innovativeness, medical importance and commercial success of new drugs.

After determining biotechnology firms' current contribution to pharmaceutical R&D productivity, an analysis of the future contribution of biotechnology firms will follow. The present study will examine the future role of biotechnology firms in reducing the R&D productivity decline by investigating whether biotechnology firms are disrupting the pharmaceutical industry. Christensen's theory of disruptive innovation will serve as a framework to assess whether biotechnology firms are disrupting the pharmaceutical industry. Following this theory, a firm can start its disruptive path by targeting low-end customers (low-end disruption) or new customers (new-market disruption). In the case of low-end disruption, customers in the low-end of the market are offered cheap drugs with low performance. Subsequently, as drug performance improves over time, the drug will increasingly appeal to the mainstream market. Since medicinal products are typically subjected to strict safety and efficacy conditions by regulatory agencies, new drugs are generally restricted from being sufficiently cheap and low in performance. Therefore, new drugs do generally not attract the low end of the market. As a result, the pharmaceutical industry is not a suitable case for studying low-end disruption. Hence, this thesis devotes no further attention to disruptive innovation at the low end of the market. Instead, the focus is on new-market disruption. As a result, research subquestion 2 states as follows:

2. ***Are biotechnology firms disrupting the pharmaceuticals market through new-market disruption?***

To answer subquestion 2, this study will analyse to what extent organisational characteristics of incumbents and entrants correspond to elements of new-market disruption. In this study, the entrants are "biotechnology" firms, and the incumbents are "pharmaceutical" firms. Since the concept of disruptive innovation is loosely defined and can be applied at different levels (such as the individual, firm or industry level), elements of the theory differ among studies (Christensen et al., 2003; Si & Chen, 2020). Elements of new-market disruption examined in this study include:

- Entrants develop new-market disruptions and thereby target unserved customers.
- Entrants cater their products to small niche markets.
- Incumbents target the most demanding (often profitable) customers.
- Incumbents "over-engineer" their products.

1.4 Hypotheses

This study will assess whether disruptive innovation by biotechnology firms contributes to a reduction in the pharmaceutical R&D productivity decline through quantitative hypothesis

testing. Table 1.1 presents an overview of the hypotheses tested in this study.

Table 1.1: **Hypotheses under investigation in this thesis.** Instead of "biotechnology firms" and "pharmaceutical firms", the hypotheses mention "firms with biotechnological organisational characteristics" and "firms with pharmaceutical organisational characteristics", which reflects how the concepts of a biotechnology firm and a pharmaceutical firm will be measured in this study. The measurement of the concepts of a biotechnology and pharmaceutical firm is described in Chapter 3.

Subquestion	**Hypothesis**	**Description**
Subquestion 1	1	Firms with biotechnological organisational characteristics have more commercial success than firms with pharmaceutical organisational characteristics.
	1.1	*Firms with biotechnological organisational characteristics generate more cumulative sales from market launch to time-to-peak sales than firms with pharmaceutical organisational characteristics.*
	1.2	*Firms with biotechnological organisational characteristics have a higher probability of developing blockbusters than firms with pharmaceutical organisational characteristics.*
	2	Firms with biotechnological organisational characteristics have a higher probability of developing innovative drugs than firms with pharmaceutical organisational characteristics.
	3	Firms with biotechnological organisational characteristics have a higher probability of developing medically-important drugs than firms with pharmaceutical organisational characteristics.
Subquestion 2	4	Firms with biotechnological organisational characteristics have a higher probability of developing drugs that address unmet medical needs than firms with pharmaceutical organisational characteristics.
	5	Firms with pharmaceutical organisational characteristics are related to developing medicines for larger patient populations than firms with biotechnological organisational characteristics.
	6	Firms with biotechnological organisational characteristics have a higher probability of targeting small niche markets than firms with pharmaceutical organisational characteristics.
	7	Firms with pharmaceutical organisational characteristics develop more over-engineered medicines than firms with biotechnological organisational characteristics.

First, this thesis will investigate the contribution of biotechnology firms to R&D productivity compared to pharmaceutical firms (research subquestion 1). The determinants of pharmaceutical R&D productivity under investigation are commercial success, innovativeness and medical importance of new medicines. I expect to find positive correlations between biotechnological organisational characteristics and commercial success (hypothesis 1), innovative drugs

(hypothesis 2) and medically-important medicines (hypothesis 3). In this thesis, commercial success will be estimated based on cumulative drug sales from market launch to time-to-peak sales and the development of blockbusters. Blockbusters are drugs that generated more than $1 billion sales in a year.

Second, this study will examine the disruptive potential of biotechnology firms by testing for the presence of elements of disruptive innovation according to disruptive innovation theory (research subquestion 2). I expect to find positive correlations between biotechnological organisational characteristics and the targeting of unserved customers by developing drugs that address unmet medical needs (hypothesis 4) and drug development in small niche markets (hypothesis 6). Moreover, I expect to find positive correlations between pharmaceutical organisational characteristics and the development of drugs that address diseases for larger patient populations (hypothesis 5) and "over-engineered" drugs (hypothesis 7). When a company "over-engineers" a drug, the company develops a drug that merely represents a marginal increase in the safety or efficacy of a pre-existing drug. The "over-engineered" drug is a sustaining innovation that serves the firm's current customers.

1.5 Research approach

Figure 1.1 presents the three stages in which I approached this study. This research commenced with examining the relevant body of literature and exploring all relevant concepts and research gaps. After I identified significant research gaps, I developed a conceptual framework. I derived multiple hypotheses from the conceptual framework. Subsequently, I developed a measure for the concepts of a biotechnology firm and a pharmaceutical firm. In the final stage, I collected and analysed data.

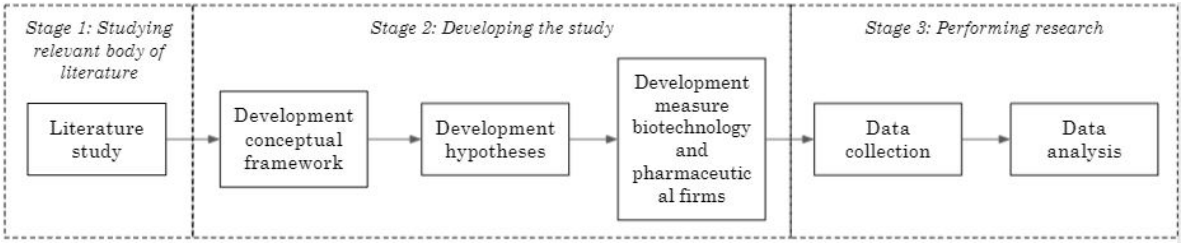

Figure 1.1: **Research approach.**

1.6 Thesis structure

The thesis structure is as follows: This chapter, introduces the scientific and practical problem under investigation, the research objective and research questions. Chapter 2 will represent a review of relevant literature regarding the relative contribution of biotechnology firms to pharmaceutical R&D productivity and its connection with the theory of disruptive innovation.

Moreover, chapter 2 will discuss the limitations of current studies and research gaps. Chapter 3 will present the research methodology used to address the research gaps. Thereafter, Chapter 4 will provide the descriptive statistics of the collected data. Chapter 5 will present the results from quantitative hypothesis testing. The following chapter, Chapter 6, will discuss the results of the quantitative analyses in the context of previous studies and their implications. Chapter 7 will conclude to what extent disruption of the pharmaceuticals market by biotechnology firms reduces the R&D productivity decline. Moreover, Chapter 7 will provide a reflection on, among others, the implications and limitations of this study and recommendations for future studies.

Chapter 2

Literature overview

This chapter has three functions: introducing and contextualising the main concepts in this study, acknowledging and reviewing relevant prior research, and exposing knowledge gaps. This chapter consists of three sections. Section 2.1 will form an introduction to the pharmaceutical R&D productivity problem. Section 2.2 will address to what extent the current body of literature has previously described the impact of biotechnology firms on pharmaceutical R&D productivity. Section 2.3 will introduce the reader to Clayton Christensen's theory of disruptive innovation and its limitations. Moreover, this section will assess to what extent current literature has applied disruptive innovation theory to the case of the emerging biotechnology sector before. The relevant research gaps exposed in this chapter will be addressed in the remainder of this thesis.

2.1 Pharmaceutical R&D productivity

This section will introduce the problem of the declining pharmaceutical R&D productivity. Section 2.1.1 will explain why R&D productivity is an important and often-used concept for assessing the viability of the pharmaceutical industry. In addition, it will resolve ambiguities concerning the interpretation of R&D productivity. The following section, section 2.1.2, will represent a description of the symptoms of the declining R&D productivity. The section thereafter, section 2.1.3, will present the causes of the R&D productivity problem. Finally, section 2.1.4 will review previous studies addressing proposed or implemented solutions to the pharmaceutical R&D productivity problem.

2.1.1 R&D productivity measure

R&D productivity is widely used as an indicator of the economic health of the pharmaceutical industry. In general, "productivity" can be defined as the *"ratio between the output volume and the volume of inputs. In other words, it measures how efficiently production input, such as*

labour and capital, are being used in an economy to produce a given level of output." (OECD, 2021). Hence, R&D productivity can be defined as the ratio between the outputs and inputs of R&D activity. While interpretations of R&D productivity vary significantly among studies, one of the most prevalent interpretations of R&D productivity is the number of new drugs per R&D spending.

Despite being widely used, the measure of R&D productivity is criticised for being flawed. Cockburn (2006) argued that productivity generally is a reasonable estimate of the performance of work that is simple and labour-intensive. However, the work performed in R&D involves complex and knowledge-intensive tasks. As a result, it is difficult to capture the actual value of inputs and outputs of R&D activities.

Besides the difficulty of capturing the value of R&D inputs and outputs, the long investment horizons of pharmaceutical R&D makes estimating productivity problematic. R&D investments in the pharmaceutical industry are generally large and upfront and have long payback times. This significant time gap between R&D investment, drug output and sales can make estimates of R&D productivity misleading (Cockburn, 2006; Hopkins et al., 2007). Some studies accommodate the time gap between R&D investment, drug output and sales in their calculations of R&D productivity (Pisano, 2006b). However, this approach is unreliable because the payback times vary among drugs. Therefore, it suffices to consider time gaps by being aware of an average time from first R&D investment to drug launch of eight to twelve years (Nightingale & Martin, 2004) and an average time from launch to peak sales of five years (IQVIA, 2017).

2.1.1.1 R&D inputs

R&D expenditure is frequently used as the sole input of pharmaceutical R&D productivity. A benefit of using R&D spending is that it is straightforward to quantify. Nevertheless, care should be taken when using R&D spending to estimate R&D productivity. Many studies fail to adjust R&D spending for inflation, and therefore, the R&D productivity presented in these studies seems worse than it is. Cockburn (2006) illustrated the impact of inflation adjustment on the change in R&D spending over time. When R&D spending of members of the PhRMA (US trade union for large pharmaceutical firms) between 1964 and 2005 is corrected for inflation using the Biomedical R&D Price Index, the increase in R&D costs changes from 12% per year to 6% per year.

The use of R&D spending as the sole input for estimating R&D productivity does not capture the actual value of the R&D input. Examples of other pharmaceutical R&D inputs are knowledge spill-overs from basic research or from being located in a technology cluster, academic technology transfer, the absorptive capacity of an organisation, the availability of state-of-the-art analytical techniques or machinery, and the talent, motivation and networks

of scientists. However, these examples of R&D inputs are difficult to quantify. As a result, these R&D inputs are not considered when estimating R&D productivity in any study.

2.1.1.2 R&D outputs

The numbers of new drugs and drug sales are often the R&D outputs investigated for estimating R&D productivity. Considering sales as an R&D output, no consensus among scholars exists on the method of quantification. Scholars typically determine sales by measuring the average sales per year of the entire industry (Pisano, 2006b; Drakeman, 2014; Pammolli et al., 2020), the peak year sales (Munos, 2009; Kneller, 2010), and the total sales of the top-selling drugs (Nightingale & Martin, 2004; Hopkins et al., 2007). Nevertheless, the use of the peak year sales and the total sales of the top-selling drugs are unreliable ways of estimating commercial performance. The peak year sales only explain 59.6% of the variance of the total sales (Fischer et al., 2010). Furthermore, the mere consideration of the total sales of the top-selling drugs fails to recognise the contribution of many small firms to commercial performance. Therefore, the most reliable estimates of drug sales are based on the total inflation-adjusted sales in the pharmaceutical industry.

Regarding using the number of new drugs as an R&D output for estimating R&D productivity, three significant issues arise. First, measuring the number of new drugs fails to consider the significant variability in new therapeutics' medical importance and innovativeness. When the medical importance and innovativeness of new drugs are considered, the decline in R&D productivity may not be as bad as it seems (Cockburn, 2006). Instead, the amount of innovative and medically-important drugs may have increased over the years, while the total number of drugs has decreased. The simultaneous increase in quality and decrease in the number of new drugs can signify that the pharmaceutical industry is increasingly focusing on more medically complex diseases, such as cancer. Second, using the number of new drugs to determine R&D productivity neglects the value of cumulative incremental improvements of therapeutics. With the terms "new drugs" or "new molecular entities" (NMEs), scholars specifically consider "drugs with a new active main ingredient". This interpretation of "new drugs" implies that only drugs with a new main ingredient are considered in determining R&D productivity. However, a fair share of drugs significantly improved due to a new dosage or formulation rather than a new main active ingredient (Cockburn, 2006). Moreover, the use of a pre-existing active ingredient to treat a new disease can also represent a significant drug innovation. Third, using the number of new drugs as an R&D output to determine R&D productivity neglects other R&D outputs, including organisational learning from failed R&D projects (Khanna et al., 2015) and other scientific and technological advancements that are not directly translated into new drugs. These R&D outputs are often left out of the estimation of R&D productivity due to their qualitative nature.

2.1.1.3 Conclusion

In conclusion, the estimation of R&D productivity is a standard approach for assessing the pharmaceutical industry's economic health. The use of R&D productivity to assess the industry's economic viability is justified because R&D productivity is one of the most important long-term drivers of the industry's financial performance (Pisano, 2006b). Moreover, it is justified in light of compatibility with the current body of research. Nevertheless, one should very carefully consider the limitations associated with estimating pharmaceutical R&D productivity. A more reliable estimation of R&D productivity can be achieved by considering inflation, time lags, the benefits of cumulative incremental improvements, and the qualitative value of new drugs in terms of medical importance and innovativeness.

2.1.2 Symptoms

The pharmaceutical R&D productivity problem has three significant symptoms. The first symptom to be discussed is the rising R&D costs. R&D costs per drug increased exponentially by 13.4% annually between 1959 and 2007 (Munos, 2009). The latest estimate of R&D costs by DiMasi (2020) is $2.8 billion per new drug (in 2018 US dollars). In contrast, in 1979, the R&D costs per new drug were $222 million (in 2018 US dollars) (Hansen, 1979). The most significant contributors to increasing R&D costs are the increase in the duration of clinical trials and attrition rates (DiMasi et al., 2003). Combined, the increase in the duration of clinical trials and attrition rates accounted for 82.5% of the total increase in costs between 1983-1994 and 1995-2007 (DiMasi et al., 2003, 2016).

The second symptom of the R&D productivity crisis is the stable new drug output. While no consensus exists on how the new drug output changed over the years, the most methodologically sound and widely adopted study revealed that the output of new drugs was stable between 1950 and 2008 (Munos, 2009). The study by Munos (2009) suggested that the chance that a company exceeds the average growth objective of two to three new drugs per year is 0.06% to 0.03%, respectively. Therefore, Munos (2009) argued, it is unlikely that companies in the pharmaceutical industry can increase their new drug output without a drastic reform of their business models. Considering the qualitative new drug output of the quantitative new drug output, Kesselheim, Wang, and Avorn (2013) suggested that, between 1970 and 2010, the discovery and development of a new medicine providing a substantial therapeutic benefit were rare. Most recently, a study by Pammolli et al. (2020) estimated the average novelty of the mechanism of action and indication of new drug candidates entering clinical trials from 2000 to 2017. The study by Pammolli et al. (2020) showed a statistically significant increasing trend in the novelty of the mechanism of action and indication of pharmaceutical R&D projects. Hence, while the quantitative new drug output may be stable (Munos, 2009), the qualitative new drug output may be increasing (Pammolli et al., 2020).

The third symptom of the decline in pharmaceutical R&D productivity is the increased occurrence of patent cliffs. Drug sales in the pharmaceutical industry are threatened by the expiration of blockbuster patents and increased "generics" penetration. The pharmaceutical industry relies heavily on the development of blockbusters (Collier, 2011). However, an increasing number of (blockbuster) drugs have been approaching their patent expiration date, without a sufficient amount of promising drugs in the pipeline (Kessel, 2011; Paul et al., 2010). Generics are therapeutically equivalent to drugs of which the patent has expired (Davit et al., 2009). When a patented drug expires, other firms often start to produce a similar drug in a generic form, which results in price competition. Since a lack of promising new drug candidates exists, the substitution of patented drugs by generic drugs puts the sales in the pharmaceutical industry at risk (Mathieu, 2008; Paul et al., 2010). Between 2010 and 2014, patent expirations were estimated to reduce sales by $209 billion per year (Paul et al., 2010). Between 2019 and 2024, patent cliffs are expected to reduce global drug sales by $198 billion and global revenues by $114 billion (EvaluatePharma, 2011).

2.1.3 Causes

Major causes of the pharmaceutical R&D productivity decline include increased attrition rates, increased duration of clinical trials, the increased focus on the development of blockbusters, regulatory hurdles and scientific and clinical challenges. The most significant contributor to the increased R&D costs is the increase in attrition rates. As an illustration, between 1983-1994 and 1995-2007, the increase in attrition rate accounted for 57.3% of the total increase in R&D expenditure (DiMasi et al., 2003, 2016). Between 2006 and 2015, regulatory agencies merely approved 9.6% of all drug candidates (Biotechnology Innovation Organization, 2016). The most important underlying causes of attrition are a lack of efficacy, clinical safety and funding, non-clinical toxicology and the rationalisation of the company portfolio (Kola & Landis, 2004; Waring et al., 2015; Hay et al., 2014; Arrowsmith, 2011a, 2011b; Arrowsmith & Miller, 2013; Fogel, 2018). The attrition rates are the lowest in clinical phase II and III (30.7% and 58.1%, respectively). At the same time, the costs of phase II and III clinical trials represent 48% of the total R&D costs (Paul et al., 2010). In phases II and III, a lack of efficacy and safety was responsible for a great majority of all failures (Arrowsmith & Miller, 2013).

The second-largest contributor to the increase in R&D costs is the duration of clinical trials (DiMasi et al., 2003, 2016). Pammolli et al. (2020) showed that between 1990 and 2013, the duration of preclinical trials, phase I clinical trials, and registration decreased, while the duration of phase II and III of clinical trials increased. The increase of the duration of phases II and III is detrimental because these clinical development phases are most expensive (Paul et al., 2010).

The increased focus on the development of blockbuster drugs is one of the causes of the decline in R&D productivity (Cockburn, 2006). Studies by Pammolli et al. (2011, 2020) showed that from 1990 to 2017, pharmaceutical R&D activities increasingly focused on the development of drugs with very high potential sales (blockbusters). The rationale behind the increased focus on the commercialisation of blockbusters, or the "blockbuster model", is that the sales from blockbusters can compensate for the high R&D costs. However, studies by Pammolli et al. (2011, 2020) also showed that, at the same time, an increasing amount of R&D activities were associated with very high levels of risk. Indeed, the prevalence of a blockbuster in a firm's R&D portfolio is often described as a random "black-swan" event (Munos, 2009; Munos & Chin, 2011). Moreover, the clinical development of blockbuster candidates is generally costly. Blockbusters are often targeted at large patient populations, and therefore, the clinical development of blockbusters requires extensive clinical trials. Hence, the increased focus on the development of blockbusters may have led to increased attrition rates and clinical development costs.

Another cause of the decline in R&D productivity is the increased burden of regulation for approving and reimbursing new drugs (Munos, 2009; Kola & Landis, 2004; Schuhmacher et al., 2016). It is argued that, since the standard of care has increased significantly over the years, regulators and society have a lower tolerance towards risk (Weatherall, 1982; Scannell et al., 2012). As a result, new drugs face higher regulatory hurdles (Hay et al., 2014), which affects both attrition rates and the duration of clinical trials.

Finally, one of the most considerable challenges in pharmaceutical R&D is the complexity of the molecular biology of the human body and our lack of understanding of it (Pisano, 2006b). The more scientists understood and had the tools to study human biology and pathology, the more complex the discovery and development of therapeutics became. Additionally, the complexity of new drug development increased as the easy targets became increasingly exhausted, and the drug industry increasingly focused on more complex diseases (Pammolli et al., 2011; Cockburn, 2006; Kola & Landis, 2004; Schuhmacher et al., 2016). The increased complexity of the discovery and development of new medicines poses significant scientific and clinical challenges. For instance, the emergence of bioinformatics tools to study diseases significantly expanded potential drug targets, while the validation of potential drug targets and the corresponding disease mechanisms remained difficult. As a result, an increasing number of drug candidates based on unvalidated drug targets enter clinical trials. The failure rates of drug candidates for new disease targets are 50% higher than for drug candidates with validated targets (Ma & Zemmel, 2002). In addition, drugs targeting new disease targets often fail in the late stages of clinical trials (Booth & Zemmel, 2004), which are more expensive (DiMasi et al., 2003).

2.1.4 Solutions

Many solutions have been proposed to solve the pharmaceutical R&D productivity problem. "Bad" solutions can be distinguished from "good" solutions. "Bad" solutions are not likely to represent a proper solution to the productivity issue according to the current body of literature, and "good" solutions are likely to solve the R&D productivity problem at least partially. "Bad" solutions are mergers and acquisitions (M&As) (LaMattina, 2011), engagement in low-risk research (Munos & Chin, 2011) and the blockbuster model (Cockburn, 2006). In contrast, "good" solutions are the adoption of open innovation models (Melese et al., 2009; Hunter & Stephens, 2010), the provision of autonomy to researchers (Cuatrecasas, 2006; Munos & Chin, 2011) and the stimulation of basic research to advance our fundamental knowledge on the molecular pathophysiology of diseases (Peck, 2007). In addition, a "good" solution is the development and improvement of tools that will allow only the most promising drug candidates to be pushed forward in clinical trials (Dmitri, 2011), such as biomarkers and animal models (Kola & Landis, 2004; Peck, 2007).

The "good" solutions have in common that implementing these solutions makes firms in the pharmaceutical industry more "biotech-like". Biotechnology firms are often small and do not have downstream capabilities, in contrast to established pharmaceutical companies. Therefore, biotechnology firms are likely to adopt open innovation models to gain access to required capabilities for the commercial development of new therapeutics (Michelino et al., 2015). Furthermore, biotechnology firms engage in more high-risk early translational research than established pharmaceutical firms (Munos & Chin, 2011). Due to their relatively organic organisational structure and entrepreneurial culture, scientists in biotechnology companies typically enjoy a high degree of autonomy (Pisano, 2006b). The high degree of autonomy in biotechnology firms is appealing to talented researchers and stimulates creativity and innovation (Cuatrecasas, 2006; Paul et al., 2010).

2.1.5 Conclusion

In this section, I introduced the symptoms, causes and solutions of the pharmaceutical R&D productivity problem. The primary symptoms of the pharmaceutical R&D productivity decline are the stable new drug output, the increasing R&D costs and the drug sales being in jeopardy due to patent expiration and generic substitution. Causes of the declining R&D productivity include increased attrition rates, increased duration of clinical trials, the increased focus on the development of blockbusters, regulatory hurdles and scientific and clinical challenges. A multitude of solutions has been proposed and implemented to solve the productivity problem. Among the solutions to the R&D productivity problem is for pharmaceutical firms to become more "biotech-like".

2.2 Impact biotechnology firms on pharmaceutical R&D productivity

Biotechnology advocates have stimulated investments, corporate strategies and policies favouring the development of the biotechnology sector (Nightingale & Martin, 2004; Hopkins et al., 2007; Malerba & Orsenigo, 2015). Significant public funding is directed to the development of biotechnology clusters and academia-industry technology transfer. Major venture capital and private equity investments are funding biotechnology startups. Pharmaceutical firms are adopting organisational strategies to mimic biotechnology organisations, such as developing isolated research-based business units that engage in risky R&D projects.

The previous section diagnosed the declining pharmaceutical R&D productivity. The following section will evaluate the advocates' claims on the promise of biotech. This section will critically review empirical evidence of the impact of biotechnology firms on five determinants of R&D productivity. The five determinants of R&D productivity are the number of new drugs per year, R&D costs, the output of innovative and medically-important new drugs and commercial success. Empirical evidence from 1950 to 2017 will be assessed. The units of analysis are biotechnology and pharmaceutical companies in the global pharmaceuticals market. An analysis of other factors that may affect the R&D productivity, such as firm size, location and institutional and policy environment, is beyond the scope of this review. Based on the literature study in this section, I will argue that biotechnology firms contribute to reducing the R&D productivity decline by improving failure rates in clinical trials and developing nearly half of all innovative and medically-important drugs.

2.2.1 New drug production

Current studies on the impact of biotechnology on pharmaceutical R&D productivity present a one-sided view. Numerous studies have estimated the impact of biotechnology on R&D productivity by assessing the changes in the rate of the production of biology-based medicines (Munos, 2009; Walsh, 2000, 2006, 2018; Grabowski & Wang, 2006).[1] Because current studies exclusively consider a technological aspect, the new biologic development, these studies neglect important organisational aspects of the emergence of biotechnology. Biotechnology has had a drastic effect on the architecture and dynamics of the drug industry. However, no previous studies reported the impact of biotechnology on pharmaceutical R&D productivity from an organisational perspective.

Besides presenting a one-sided view of the emergence of biotechnology, previous studies have mistakenly drawn conclusions on the effect of biotechnology firms based on the new biological

[1] Biology-based medicines are also referred to as biologics, biopharmaceuticals or new biological entities (NBEs).

drug output. The rate of new biologics development is not the same as the new drug output of biotechnology firms. Initially, biotechnology firms exclusively developed biologics, but nowadays, biotechnology and pharmaceutical companies develop both chemistry-based[2] and biology-based medicines. For instance, between 1998 and 2007, more than one-third of the biopharmaceuticals were developed by pharmaceutical firms and over one-fourth of the small molecules were developed by biotechnology firms (Kneller, 2010). However, no comparative analysis of the contributions of biotechnology and pharmaceutical firms to new drug output is published yet.

Based on current studies, it cannot be said whether biotechnology firms improved the output of new drugs per year. Despite the lack of empirical evidence, Kneller (2010) argued that the contribution of biotechnology firms is positive. According to Kneller (2010), the total drug output would be substantially lower without the contribution of biotechnology firms. However, I argue that it may not be true that the total drug output would be substantially lower without the contribution of biotechnology firms. Pharmaceutical firms may have lowered their drug innovation efforts in response to the innovative efforts of biotechnology firms. It can be rational for pharmaceutical firms to leave the high-risk, innovative activities to biotechnology firms. Pharmaceutical companies can use their financial resources to acquire promising drug candidates through M&As with biotechnology firms (Drakeman, 2014).

2.2.2 R&D costs

To understand how biotechnology firms influence pharmaceutical R&D costs, it is important to know how biotechnology firms affect the failure rates and duration of clinical trials. The increase in failure rates and duration of clinical trials are the most significant contributors to the increase in R&D costs (DiMasi et al., 2003). However, no convincing evidence currently exists on the impact of biotechnology firms on R&D costs in terms of lowering the duration of clinical trials. While between the 1970s and 1990s, the duration of clinical trials increased, in recent years, the duration of clinical trials witnessed a decrease (Hopkins et al., 2007). Nevertheless, it is questionable whether this recent decrease in the duration of clinical trials can be attributed to the emergence of biotechnology firms. Hopkins et al. (2007) claimed that biotechnology firms did not positively contribute to the duration of clinical trials because the significant bottleneck in drug innovation shifted rather than disappeared. Formerly, the synthesis and identification of new drug candidates hampered drug innovation. The emergence of biotechnology firms merely shifted the bottleneck of the drug innovation process to the validation and characterisation of new drug candidates. Furthermore, Hopkins et al. (2007) argued that: *"[The decrease in the duration of clinical trials] may not necessarily be early evidence of the impact of biotechnology, as the regulatory landscape changed during the 1990s due to accelerated approval and fast-tracking and management practices, especially in large*

[2]Chemistry-based medicines are also referred to as small molecules or new chemical entities (NCEs).

firms, have improved over the same period.".

Biotechnologies and biotechnology firms seemed to previously impair (Hopkins et al., 2007; Pisano, 2006b) but recently improved clinical failure rates (Pammolli et al., 2020). Hopkins et al. (2007) and Pisano (2006b) argued that the emergence of biotechnology, particularly genomics technologies, impaired success rates in clinical trials. Hay et al. (2014) showed that small biotechnology firms generally develop more risky drugs based on unvalidated disease targets than pharmaceutical firms. As previously described, drug candidates based on unvalidated disease targets are associated with high failure rates late in the clinical development process (Ma & Zemmel, 2002; Booth & Zemmel, 2004). Therefore, Hopkins et al. (2007) and Pisano (2006b) argued that biotechnology negatively affects R&D productivity, at least in the short term. However, a recent study by Pammolli et al. (2020) showed that, between 2000-2009 and 2010-2013, the failure rates in preclinical research and all phases of clinical trials decreased. Further investigation by Pammolli et al. (2020) revealed that the R&D projects of biotechnology firms are responsible for a significant fraction of the decrease in failure rates in clinical trials. Pammolli et al. (2020) argued that an increased understanding of diseases' biological foundation can explain the recent improvements in failure rates.

2.2.3 Innovativeness and medical importance of new drugs

Kneller (2010) showed that biotechnology firms develop relatively more innovative and medically-important drugs than pharmaceutical firms. Of all drugs discovered by biotechnology firms from 1998 to 2007, 68% was scientifically novel, and 65% represented a significant improvement over current therapies. In contrast, of all drugs discovered by pharmaceutical companies, only 35% was scientifically novel, and 38% represented a significant improvement over current therapies.

Biotechnology companies were responsible for the development of a considerable share of innovative medicine and medically-important medicines, which can be explained by the large degree of technology transfer from academia to biotechnology firms. Kneller (2010) suggested that, between 1998 and 2007, biotechnology firms discovered only a small share of the total amount of innovative and medically-important drugs. Biotechnology firms merely discovered 25% and 23% of the scientifically novel drugs and drugs that represent a significant improvement over current therapies, respectively. However, biotechnology firms developed a considerable fraction of the innovative and medically-important drugs. Biotechnology firms were responsible for the initial development of 48% and 44% of all scientifically innovative drugs and drugs that represent a significant improvement over current therapies, respectively. The difference between the number of drugs discovered and developed by biotechnology firms can be explained by the fact that biotechnology firms licensed many university-discovered drugs. Biotechnology firms licensed 74% and 70% of the university-discovered drugs that

were scientifically innovative and represented a significant improvement over current therapies, respectively.

The high degree of technology transfer from academia to biotechnology firms can be explained by biotechnology firms closing the so-called translational research gap (Pisano, 2006b). The science and technology offered by universities can be too "basic" for pharmaceutical firms. Pharmaceutical firms may not be interested in performing basic and translational research or may not have the right internal capabilities. In contrast, research performed in biotechnology firms closes the gap between research that is too "applied" for universities and too "basic" for pharmaceutical companies. Another explanation for the high degree of technology transfer from academia to biotechnology firms is the relative financial attractiveness for scientists to spin out to a biotechnology startup. By licensing intellectual property to pharmaceutical firms, scientists can gain royalties that have to be shared with the university. Instead, by establishing a biotechnology startup, university scientists dream of gaining millions of dollars worth of equity.

2.2.4 Commercial success

Biotechnology firms generally have not been commercially successful. Commercial performance can be measured in many ways, such as based on a firm's sales, revenues or profits. Previous studies estimated the commercial success of biotechnology firms by measuring the average sales per year (Pisano, 2006b; Drakeman, 2014; Pammolli et al., 2020), the peak year sales (Munos, 2009; Kneller, 2010) and the profitability (Pisano, 2006b). Between 1985 and 2004, the sales per dollar spent on R&D of pharmaceutical firms was consistently higher than biotechnology firms (Pisano, 2006b). Moreover, between 1975 and 2004, almost no biotechnology firm has been profitable (Pisano, 2006b; Malerba & Orsenigo, 2015).[3] A great majority of the biotechnology firms has even never had positive cash flows despite being in business for more than ten years. However, no recent studies on the commercial performance of biotechnology firms exist.

2.2.5 Conclusion

This section assessed to what extent current literature supports the idea that the emergence of biotechnology firms can improve the pharmaceutical R&D productivity decline. Current studies suggested that biotechnology firms significantly contribute to the production of innovative and medically-important drugs, which can be attributed to their close ties to universities. Moreover, biotechnology firms significantly contributed to recent improvements in the clinical failure rates, which was one of the main drivers in the increase of R&D costs. However, no

[3]Notable exceptions of profitable biotechnology firms are Amgen and Genentech, which were responsible for 53% of the total cash flow of all biotechnology firms (Pisano, 2006b).

conclusions can be drawn based on current empirical evidence on another significant driver of R&D costs: the duration of clinical trials. Additionally, no conclusions can be made regarding the impact of biotechnology firms on new drug production. Finally, based on current studies, biotechnology firms seem to have worse commercial performance than pharmaceutical firms. However, these studies may be outdated. Therefore, future investigation of the comparative performance of biotechnology firms in new drug production, the duration of clinical trials, and commercial success can provide additional insights into the impact of biotechnology firms on R&D productivity.

Another conclusion that is drawn from reviewing studies on the impact of biotechnology firms on R&D productivity is that these studies lack a theoretical grounding. To examine the future contribution of biotechnology firms to R&D productivity, the current body of literature can benefit from positioning its findings in a theoretical framework. A theoretical basis could provide a means to obtain new insights into the potential effect of biotechnology firms on pharmaceutical R&D productivity.

2.3 Disruptive innovation

The previous section presented current evidence of the impact of biotechnology firms on pharmaceutical R&D productivity. One conclusion was that the current body of literature can benefit from having a theoretical basis. This thesis will use disruptive innovation to complement empirical findings and examine the disruptive potential of biotechnology firms in the pharmaceutical industry. The following section will present an introduction to disruptive innovation theory, its limitations and to what extent management scientists applied the theory of disruptive innovation to the case of the emerging biotechnology sector before.

2.3.1 Disruptive innovation theory

The theory of disruptive innovation describes the impact of technological change and innovation on companies, industries, and society (Christensen, 1997; Christensen, Baumann, Ruggles, & Sadtler, 2007). As first described by Bower and Christensen (1995), disruptive innovation theory is the paradoxical idea that leading firms fail because they serve their current customer base well. The theory is further expanded by Christensen in, among others, the books The Innovator's Dilemma (Christensen, 1997) and The Innovator's Solution (Christensen et al., 2003). It has become one of the most influential business ideas of the 21st century. Important inspirations for the development of Christensen's theory of disruptive innovation were studies by Tushman and Anderson (1986) and (Henderson & Clark, 1990), which proposed alternative explanations for the failure of leading firms. Similar to Schumpeter's creative destruction (1942), the theory of disruptive innovation recognises the role of technological innovations and entrepreneurial firms - often new and small - in shaking up

the market (Spencer & Kirchhoff, 2006). Christensen's disruptive innovation explains processes by which creative destruction can occur on a meso- and microeconomic theoretical level (Christensen, 1997; Schneider, 2017). Moreover, Christensen's theory of disruptive innovation provides firms with strategic management insights on identifying and dealing with disruptive innovations. Finally, the theory of disruptive innovation addresses several important aspects of innovation theory that other theories left unsolved, such as business models innovations (Christensen et al., 2003; Kawamoto & Spers, 2019).

The theory of disruptive innovation contradicts the previously prevalent idea that leading firms fail because they are not aware of the technological advancements in their market. Instead, the theory states that leading firms are aware of the disruptive innovations. However, it is not rational for the established firms to invest in these innovations. Disruptive innovations are generally first used in small or emerging markets, generate lower profits and do not provide additional value for the most profitable customers (Christensen, 1997). Therefore, instead, leading firms typically engage in sustaining innovations. Sustaining innovations result in incrementally better products or services for the established market. By increasingly improving the products or services for the established market, the leading firms ultimately overshoot the mainstream customer demand (Figure 2.1) (Christensen, Anothy, & Roth, 2004).

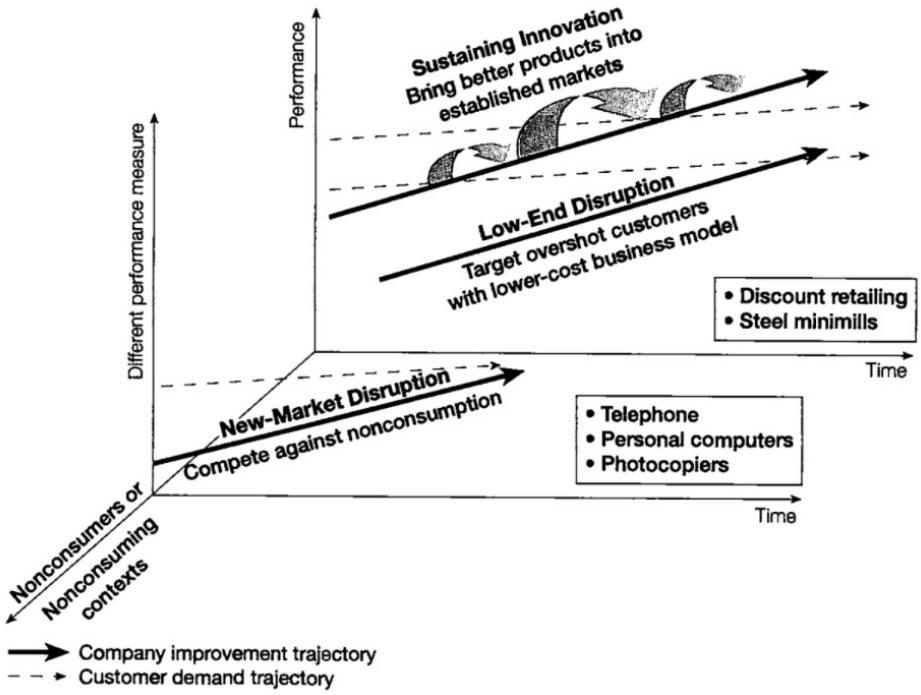

Figure 2.1: **Disruptive innovation theory** (Christensen et al., 2003).

Two types of disruptive innovation processes are low-end and new-market disruption (Figure 2.1) (Christensen et al., 2003). In the case of low-end disruption, the performance of the innovation of the entrant is initially inferior. However, after some time, the performance of

the innovation increases. While the product or service of the leading firm is overshooting the mainstream customer demand, the product or service of the entrant is increasingly appealing to the mainstream market. As a result, the entrant will replace the former leading firm. In the case of new-market disruption, the disruptive innovation appeals to previously unserved customers in a new market. The performance of the disruptive innovation is different from the performance of the incumbent product or service and, therefore, cannot be compared using the same performance measure.

From a strategic management perspective, understanding the mechanisms by which technological innovations can disrupt the market helps firms identify when competitors are developing disruptive innovations (Christensen et al., 2004). In addition, understanding the mechanism by which technological innovations can disrupt the market exposes business opportunities. As a result, insights from disruptive innovation theory are important for established firms to maintain their market share and for entrants to gain market share. The key lesson learned from the theory of disruptive innovation is that a firm should not be too focused on serving its current customer base. A firm should not exclusively focus on its most demanding customers because it results in negligence of disruptive innovations and thereby jeopardises future growth.

2.3.2 Limitations

Scholars devoted much research efforts to exposing limitations and proposing improvements to the theory (Christensen et al., 2008). Important debates considered, among others, the interpretation of the term "disruptive innovation" (Danneels, 2005; Markides, 2005; Bergek et al., 2013), the predictive capacity of the theory (Christensen et al., 2004; Danneels, 2005; Christensen et al., 2007; Govindarajan & Kopalle, 2005; Raynor, 2011) and the generalisability of the theory to other firms and industries (Christensen et al., 2004; King & Baatartogtokh, 2015). Moreover, important improvements and nuances regarded, for instance, how firms deal and should deal with disruption (Christensen et al., 2003; Gilbert, 2005; Kapoor & Klueter, 2014; O'Reilly & Tushman, 2016), and what the trajectory of the performance of disruptive innovation looks like (Christensen & Bower, 1996; Adner, 2002; Sood & Tellis, 2006; Adner & Kapoor, 2016; Christensen & Sundahl, 2016).

Lepore (2014) and King and Baatartogtokh (2015) criticised the rigorousness and generalisability of the theory of disruptive innovation. Lepore (2014) challenged the methodological design that Christensen used to prove his theory. Lepore (2014) argued that Christensen cherry-picked the examples used to substantiate the theory of disruptive innovation. In her argumentation, Lepore (2014) disproved disruptive innovation theory by applying the theory to other cases. Therefore, Lepore (2014) claimed, the theory of disruptive innovation lacks generalisability and cannot be used to understand or predict the impact of new technologies

in other cases. Nevertheless, the study by Lepore (2014) was also criticised for handpicking examples that do not definitively disprove the theory (Oremus, 2015).

King and Baatartogtokh (2015) argued that predictions from disruptive innovation theory can be used as a warning sign but should never replace making a thoughtful analysis. King and Baatartogtokh (2015) assessed the theory's validity and generalisability by testing whether 77 applications of disruptive innovation theory, as described in the books The Innovator's Dilemma (Christensen, 1997) and The Innovator's Solution (Christensen et al., 2003), match the theory's principles. From this assessment, King and Baatartogtokh (2015) found that only 9% of all 77 case studies fit the conditions or predictions of the theory of disruptive innovation.

2.3.3 Applications to drug innovation

Merely two studies that connect the theory of disruptive innovation to the dynamics between pharmaceutical firms and biotechnology companies exist (Kapoor & Klueter, 2014; Birkinshaw et al., 2018). This is remarkable because disruptive innovation theory has been applied to hundreds of cases already, including cases in the healthcare industry (Christensen et al., 2000, 2008; Hwang & Christensen, 2008). The two studies connecting disruptive innovation theory to biotechnology-pharmaceutical firm dynamics do so to a limited extent. Birkinshaw et al. (2018) investigated how established pharmaceutical companies respond to potentially disruptive innovations of biotechnology firms under the assumption that disruptive innovation occurs. Thereby, Birkinshaw et al. (2018) left an important question, whether biotechnologies can be disruptive innovations, unanswered. Kapoor and Klueter (2014) investigated the organisational inertia in resource allocation of pharmaceutical incumbents adopting the disruptive innovation gene therapies. Kapoor and Klueter (2014) argued that gene therapy is a disruptive innovation since it is a radically new technology and demands a new business model. *"[Gene therapy] represents a disruptive technological regime because gene therapies are typically one-off or significantly less frequent customised treatments, resulting in major challenges in pricing and reimbursement"* (Kapoor & Klueter, 2014). The argumentation why gene therapy is a disruptive innovation neglects multiple aspects of disruptive innovation, such as the following of a disruptive performance trajectory.

More generally, the concept of disruptive innovation has been applied to drug discovery and development in several instances. According to literature, disruptive innovations in the drug industry are direct-acting antivirals (Klein, 2019), human induced pluripotent stem cells (Vos et al., 2016), the addition of sodium-glucose cotransporter 2 inhibitors to armamentarium in chronic kidney disease treatments (Norton & Star, 2020), and gene therapies (Kapoor & Klueter, 2014; Ahn et al., 2019). However, these innovations are arguably not disruptive because it is questionable whether they follow a disruptive path. Medicines cannot follow a

disruptive path because the diffusion of a drug from one market to another is governed by chance instead of performance improvements. A drug treating one disease cannot compete with a drug treating another disease. Moreover, in the rare event that diffusion of a drug from one market to another occurs, the use of an old drug to treat a new disease will be a sustaining innovation rather than a disruptive innovation. Medicines will not fundamentally change the pharmaceutical industry, but rather their underlying technologies or business models will. In addition, the technologies identified as disruptive innovations in literature do not seem to follow a disruptive path because they were not overlooked by incumbents and did not diffuse into mainstream markets due to technology improvements (Klein, 2019; Vos et al., 2016; Kapoor & Klueter, 2014; Ahn et al., 2019). Hence, while technologies and business models can be disruptive innovations in the drug industry, it is not evident that instances of disruptive innovations previously occurred.

2.3.4 Conclusion

This section introduced the theory of disruptive innovation and its limitations. This theory is subject to continuous refinements and extensions. Particularly questioned is to what extent the theory of disruptive innovation can be applied in different contexts and used as a prediction tool. The review of applications of disruptive innovation theory to biotechnology-pharmaceutical firm dynamics and the drug industry begs the question of whether disruptive innovation can occur in the pharmaceutical industry. Although the theory of disruptive innovation has been applied to numerous cases, merely two limited applications to biotechnology-pharmaceutical firm dynamics exist in the literature. Moreover, arguably no previous instances of disruptive drug innovations can be found. Therefore, the application of the theory of disruptive innovation to the case of the emerging biotechnology sector and the drug industry, in general, can progress our knowledge on its generalisability and predictive capacity.

Chapter 3

Methodology

This chapter will present the methodology used for analysing whether new-market disruption by biotechnology firms can reduce the pharmaceutical R&D productivity decline. This chapter will encompass the definition of biotechnology and pharmaceutical firms (section 3.1) and the operationalisation of variables (section 3.2). Furthermore, this chapter will cover the sampling (section 3.3) and data collection approach (section 3.4), and the methodologies used for sales calculation (section 3.5) and statistical modelling (section 3.6).

3.1 Definition biotechnology and pharmaceutical firms

In contrast to current studies, I did not classify firms into "biotechnology firms" and "pharmaceutical firms" due to the ambiguity and inconsistency of their definitions. Instead of strictly speaking of "biotechnology" or "pharmaceutical" companies, organisational characteristics denoted whether a firm resembles a biotechnology or a pharmaceutical firm.

According to literature, a biotechnology firm is a new firm (incorporated after 1976) (Drakeman, 2014) and often, a spin-out from a university, public research institute or hospital (Grabowski & Vernon, 1994).[1] Biotechnology firms typically locate themselves in regional bioclusters, where the companies are close to organisations with complementary assets, universities and venture capitalists (Cooke, 2003; Nosella et al., 2005). Biotechnology firms are specialised and research-focused because their initial aim is to perform the early development of a promising new invention (Nosella et al., 2005). These inventions are developed using cutting-edge science and technology, and therefore, their further development is associated with high levels of uncertainty and risk (Munos & Chin, 2011). On top of that, biotechnology firms typically perform the early clinical development of new drug candidates, associated with low probabilities of success. Therefore, biotechnology firms typically perform risky R&D projects. Because

[1] Firms that spun out of a universities, public research institutes or hospitals will be referred to as academic spin-outs.

biotechnology firms generally focus on the early clinical development of the invention and lack downstream capabilities, such as late-stage clinical development, manufacturing and marketing, biotechnology firms are forced to collaborate with firms with complementary capabilities (Grabowski & Vernon, 1994; Cockburn, 2004; Pisano, 1990; Crispeels et al., 2015). Hence, based on literature, the definition of a biotechnology firm is a relatively new firm that is spun out of academia, located in a biocluster, specialised and research-focused, collaborative and engaged in risky R&D.

In contrast to biotechnology firms, pharmaceutical firms are generally old and established firms with roots in pharmacies and chemical companies (Grabowski & Vernon, 1994). These firms are not necessarily located in bioclusters (Cooke, 2003). Pharmaceutical firms typically have broad and diversified R&D portfolios and capabilities along the entire value chain, from discovery to distribution (Henderson & Cockburn, 1996; Grabowski & Vernon, 1994; Cockburn, 2004). Due to the declining R&D productivity and emergence of entrepreneurial biotechnology firms, pharmaceutical firms shy away from investing in R&D projects with high levels of uncertainty (Munos & Chin, 2011). Examples of R&D projects with high levels of uncertainty are drug candidates in a therapeutic area with a low probability of success and discovery and early clinical development activities. Instead of performing R&D projects in collaboration with other firms, pharmaceutical firms often obtain complementary capabilities or promising drug candidates or targets via M&As (Pisano, 1990). Hence, based on literature, the definition of a pharmaceutical firm is a relatively old firm that is not spun out of academia, not located in a biocluster, not particularly collaborative or engaged in high-risk R&D, vertically integrated and has a broad R&D project portfolio.

Based on the descriptions of biotechnology and pharmaceutical firms in the literature, I initially defined biotechnology and pharmaceutical firms in this study based on seven organisational characteristics. The seven organisational characteristics used to define biotechnology and pharmaceutical firms were the age, location, origin, position in the value chain, specialisation, riskiness of R&D projects and collaboration. I evaluated the reliability of using these seven organisational characteristics based on an internal consistency analysis and inter-item correlations. The reliability analyses showed that the internal consistency of the seven organisational characteristics is unacceptable and that the characteristics very poorly measure the same concept (Appendix A). To improve the reliability of the definitions of biotechnology and pharmaceutical firms, I excluded the organisational characteristics with negative inter-item correlations, which were location, riskiness of R&D projects and collaboration. Subsequently, I performed reliability analyses to test the reliability of the remaining organisational characteristics (age, origin, specialisation and position in the value chain) in defining biotechnology and pharmaceutical companies. The exclusion of location, riskiness of R&D projects and collaboration significantly increased the internal consistency from a Cronbach's alpha <0.3 to

a Cronbach's alpha of around 0.6 (Appendix A.2). A Cronbach's alpha of 0.6 is a moderate level of internal consistency (Hair et al., 2003). This result suggests that the location, riskiness of R&D projects and collaboration organisational characteristics do not reliably measure the concept of being a biotechnology or a pharmaceutical firm. Moreover, it indicates that the organisational characteristics of age, origin, position in the value chain and specialisation measure the same concept to a moderately reliable extent. Therefore, while I analysed all seven organisational characteristics, I will only present the analyses of a firm's age, origin, position in the value chain and specialisation.

I excluded some important characteristics from the analysis due to a lack of publicly available data, such as organisational structure and culture (Pisano, 2006b; Munos & Chin, 2011; Audretsch, 2001; Garnier, 2008). The organisational structure of a biotechnology firm is typically flatter than a pharmaceutical firm. The culture of a typical biotechnology firm is entrepreneurial, which causes the scientists to enjoy a high degree of autonomy. In contrast, the organisational structure of a pharmaceutical firm is typically more hierarchical. Strategic decision-making typically takes place in top management, and therefore, scientists enjoy less autonomy. Future studies can improve the reliability of the measures of biotechnology and pharmaceutical firms by incorporating the excluded organisational characteristics.

3.2 Variables

The main concepts investigated in this thesis are organisational characteristics, R&D productivity and new-market disruption. I delineated the concept of organisational characteristics into four specific organisational characteristics: age, origin, position in the value chain and specialisation. I analysed the concept of pharmaceutical R&D productivity based on the commercial success, innovativeness and medical importance of medicines. I excluded other determinants of R&D productivity, such as costs, attrition rates and duration of clinical trials, from the analysis due to a lack of publicly available data. I analysed the concept of new-market disruption based on four aspects: new-market development, targeting the mainstream market, targeting small niche markets and over-engineering drugs. I excluded aspects of new-market disruption because these elements require rich data collected using in-depth qualitative research, which is beyond the scope of this study. Notable excluded elements of new-market disruption are the following (Si & Chen, 2020; Govindarajan & Kopalle, 2005):

- The incumbents are aware of the disruptive innovation and deliberately do not invest in the particular disruptive innovation.
- The entrants displace the incumbents due to new-market disruption.
- New-market disruptions are "good enough" - better than nothing.
- The disruptive innovation creates entirely new value networks.

3.2.1 Independent variables

3.2.1.1 Age

A firm's age is among the distinguishing features of biotechnology and pharmaceutical firms. The first biotechnology firm, Genentech, was incorporated in 1976. Since 1976, thousands of new biotechnology firms have been established. Therefore, some studies distinguished between old and new firms based on whether the firms were established before and after 1976, respectively (Munos, 2009). Some studies even distinguished between biotechnology and pharmaceutical firms based on whether the firms were incorporated before or after 1976 (Drakeman, 2014). In this study, each firm obtained a score of 1 when founded after 1976 and a score of 0 when founded before 1976. I averaged the scores of all firms involved in a particular stage of drug development and commercialisation. The resulting scores constituted the continuous variable *Age*.

3.2.1.2 Origin

Biotechnology firms generally have two origins: a university, public research institute or hospital, and a pharmaceutical firm (Pisano, 2006b). Although biotechnology firms do not exclusively originate from academia, research institutes or hospitals, it is coined as one of the defining features of a biotechnology firm in literature (Grabowski & Vernon, 1994). In this study, a firm obtained a score of 1 when at least one of its founders was affiliated with a university, hospital or research institute directly before founding the company and a score of 0 when it was not. I averaged the scores of all firms involved in a particular stage of drug development and commercialisation. The resulting scores constituted the continuous variable *Origin*.

3.2.1.3 Position value chain

A biotechnology firm typically focuses on translational research and early drug development, while a pharmaceutical firm is typically vertically integrated. Therefore, the position in the value chain is among the distinctive features of biotechnology and pharmaceutical firms. A firm obtained a score of 1 when the company mainly focused on discovering and developing new drugs. A firm obtained a score of 0 when it focused also or exclusively on downstream activities, such as manufacturing. I averaged the scores of all firms involved in a particular stage of drug development and commercialisation. The resulting scores constituted the continuous variable *Position Value Chain*.

3.2.1.4 Specialisation

A biotechnology firm typically focuses on developing and commercialising medicines in a particular therapeutic area or a proprietary technology platform (Pisano, 2006a). In contrast,

pharmaceutical firms typically develop a broad scope of R&D projects in many different therapeutic areas or technologies. Hence, there is a distinctive difference between the extent to which biotechnology and pharmaceutical firms are specialised. A firm obtained a score of when the company focused on one or two therapeutic areas or one technology platform, and if not, a firm obtained a score of 0. I averaged the scores of all firms involved in a particular stage of drug development and commercialisation. The resulting scores constituted the continuous variable *Specialisation*.

3.2.2 Dependent variables

3.2.2.1 Commercial success

I measured commercial success in two ways: by considering the cumulative sales from market launch to time-of-peak sales and by assessing whether or not a drug has achieved blockbuster status.[2] A drug obtains blockbuster status when the drug generates more than $1 billion annually. The methodology used to calculate the cumulative sales from market launch to time-of-peak sales will be described in section 3.5. The cumulative sales from market launch to time-of-peak sales of drugs constituted the continuous variable *Cumulative sales*, which has the unit of millions of inflation-adjusted 2021 US dollars. I used the dummy variable *Blockbuster* to operationalise whether drugs obtained blockbuster status. A drug obtained a score of 1 when the drug obtained blockbuster status and 0 when the drug did not.

3.2.2.2 Medical importance

I estimated the medical importance of new drugs based on whether a drug obtained priority or standard review designation from the FDA. The priority review designation program aims to stimulate innovation by accelerating FDA approval from ten months, on average, to a maximum of six months. A drug obtains a priority review designation by the FDA when the drug provides *"significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to standard applications"* (US Food and Drug Administration, 2018b). I used the dummy variable *Standard or priority review* to operationalise whether a drug was medically important or not. A drug obtained a score of 1 when the drug obtained FDA priority review designation and a score of 0 when the drug obtained FDA standard review designation.

While convenient to use, it should be noted that the use of the measure of priority review designations has two significant limitations. First, obtaining a priority review designation is an indirect measure of medical importance and is governed by policy and human decision-making. While requirements for obtaining a priority review designation did not change in the

[2]It should be noted that ultimately, profits rather than sales are important for the pharmaceutical industry's economic health. Unfortunately, no data on the profitability of drugs were publicly available.

time frame under investigation in this study (Kepplinger, 2015), the FDA's rate of postapproval revisions of priority review designations suggests that the priority review designation process contains inherent deficits (Berlin, 2009). Second, a secondary market for priority review designation vouchers exists, which means that some drugs may have a priority review designation without representing a significant improvement compared to existing treatments (Robertson, 2016). The only drug included in this study that I falsely annotated as a medically-important drug due to the secondary priority review voucher market was Praluent (alirocumab by Regeneron Pharmaceuticals and Sanofi) (Loftus, 2015).

3.2.2.3 Innovativeness

I estimated the innovativeness of a new drug based on whether the drug was first in class. A drug is a first-in-class drug when the drug uses *"a new and unique mechanism of action for treating a medical condition."* (Lexchin, 2016). According to Lanthier, Miller, Nardinelli, and Woodcock (2013): *"Although subsequent approvals within the same class may prove to have advantages over the first drug, first-in-class drugs are genuinely innovative, because each represents a novel approach to drug therapy."* I used the dummy variable *First-in-class drugs* to operationalise whether a drug was first-in-class. A drug obtained a score of 1 when the drug was first-in-class and 0 when the drug was not.

3.2.2.4 New-market development

I determined whether a drug was commercialised on a new market based on whether the drug fulfilled a previously unmet medical need. I used the dummy variable *Fast Track* to operationalise whether a drug addressed a previously unmet medical need. A drug obtained a score of 1 when the drug obtained FDA Fast Track designation and 0 when the drug did not. Drugs that obtain Fast Track designation *"treat serious conditions and fill an unmet medical need"* (US Food and Drug Administration, 2018a). Similar to FDA priority review designations, the obtaining of an FDA Fast Track designation is an indirect measure and is governed by policy and human decision-making. Between 2008 and 2015, the formal conditions for obtaining Fast Track designation did not change (Kepplinger, 2015).

3.2.2.5 Targeting the most demanding market

I determined the extent to which a drug targets the mainstream market based on the patient population of the disease a drug addresses. For simplicity, I only considered the US patient population. The US patient populations of the diseases that the drugs address constituted the continuous variable *Patient population*.

3.2.2.6 Targeting niche markets

I determined whether a drug targets a small niche market based on whether the drug is an orphan drug. An orphan drug is a drug that treats a rare disease or condition (affecting less than 200.000 people in the US) (US Food and Drug Administration, 2020). I used the dummy variable *Orphan drugs* to operationalise whether a drug targets a small niche market. A drug obtained a score of 1 when the drug is an orphan drug and 0 when the drug is not.

3.2.2.7 Over-engineered drugs

When a company "over-engineers" a drug, the company further develops a drug in a way that does not represent a significant improvement, such as in terms of safety and efficacy. The dummy variable *Over-engineered drugs* consists of two groups of new drug applications (NDAs): a group of "over-engineered" NDAs and a group of medically-important drugs. The group of medically-important drugs consists of new drugs that obtained FDA priority review designation. The group of "over-engineered" NDAs consists of the FDA approvals obtained for a new active ingredient, a new dosage form, a new combination of drugs, a new formulation or manufacturer and a new indication that do not represent a significant improvement over pre-existing treatments. A drug obtained a score of 1 when it belongs to the group of medically-important drugs and 0 when it belongs to the group of "over-engineered" NDAs.

3.2.3 Controlling variable

3.2.3.1 Small molecules or biological drugs

I controlled every relationship in all statistical analyses for whether a drug was a small molecule or a biologic. I adjusted for whether a drug was a small molecule or a biologic to separate the biotechnological factor from the organisational factors that play a role in the relationship between biotechnology firms and R&D productivity. I used the dummy variable *Small molecule or biologic* to operationalise whether a drug was a small molecule or a biologic. A drug obtained a score of 1 when the drug was a biologic and 0 when the drug was a small molecule.

3.3 Sample

I analysed the pharmaceutical industry on the R&D project level. The focus on the project level avoids some of the bias that exists due to heterogeneity among drug-developing firms. For instance, by performing analyses on the project level, an analysis of the commercial success of R&D projects can be made without using controlling variables such as firm size in statistical analyses.

I used two samples in this study. The first sample consists of all FDA-approved NMEs between

2008 and 2015 (Figure 3.1). I used this sample for testing hypotheses 1 to 6. I excluded NMEs that were not drugs from the sample (Appendix B). An example of an NME that is not a drug is an imaging agent for performing MRI scans. The second sample consists of all FDA-approved NDAs for a new active ingredient, a new dosage form, a new combination of drugs, a new formulation or manufacturer, and a new indication between 2008 and 2015 (Figure 3.1). From this sample, I excluded NDAs that were not drugs (such as medical gas) and were already marketed, NDAs of which the company was not a drug company, and NDAs for which no information was provided (Appendix C). I used both sample 1 and sample 2 for testing hypothesis 7.

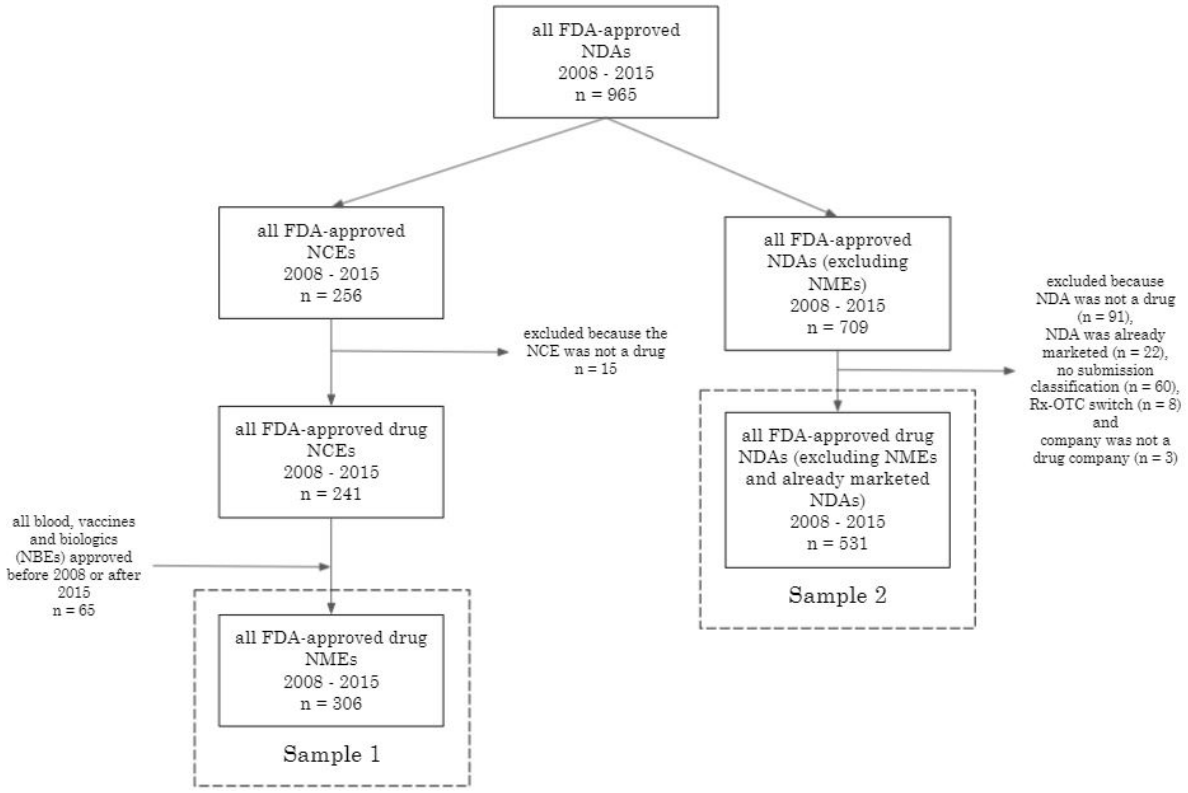

Figure 3.1: **Samples for data collection.** Sample 1 was used to test hypotheses 1 to 6, and sample 2 was used to test hypothesis 7.

As previously mentioned in the literature study (section 2.1.1.2), current studies have failed to acknowledge the value of cumulative incremental improvements in drug innovation. A change in dosage or a different formulation can significantly affect the performance of a drug (Cockburn, 2006). Nevertheless, in this study, I deliberately chose to split the NDAs that are new drugs (sample 1) from the NDAs that are additions to existing drugs (sample 2) into two different samples. The differences in the underlying process of developing new drugs and developing additions to existing drugs complicate the interpretation of the results and diminish its meaningfulness.

I chose to collect data from 2008 to 2015 because of two reasons. First, this study aims to build upon the study by Kneller (2010), whose timeframe of data collection was from 1998 to 2007. Second, limiting the data collection until 2015 enables the collection of peak sales data. On average, peak sales are reached within five years after market launch (Fischer et al., 2010).

I limited the samples to NDAs approved by the FDA for two reasons. First, NDAs approved by the FDA are a good representation of the NDAs approved globally (Kneller, 2010). FDA-approved NDAs provide a good representation because, even though a drug was not developed in the US, many drug-developing countries worldwide will still apply for an NDA in the US. Having an FDA-approved NDA is desirable for a drug-selling firm because the US holds the largest share in the pharmaceuticals market by far. In 2020, the US was responsible for 48% of global sales in the pharmaceutical industry (Statista, 2021). Therefore, although the samples are limited to NDAs approved in the US, the samples are a good representation of global NDAs. Second, it is convenient to restrict the samples to FDA-approved NDAs because the US government provides a relatively large amount of publicly available data, such as data on clinical trials and corporate financial statements.

3.4 Data

I obtained the trade name, active ingredient, submission classification, FDA applicant and priority or standard review status of all NDAs approved by the FDA between 2008 and 2015 from the Drugs@FDA Database of the Center for Drug Evaluation and Research (CDER) (US Food and Drug Administration, 2021a). I split the NDAs into a sample containing all NCEs (sample 1) and a sample containing all NDAs except for the NCEs (sample 2). The NDAs in sample 2 include approvals for a new active ingredient, a new dosage form, a new combination of drugs, a new formulation or manufacturer and a new indication. Excluded from the sample were NDAs that were not drugs and were already marketed or lacked information on the type of NDA or review designation.

I collected data of whether the NCEs (sample 1) are a small molecule or biologic, obtained priority review and Fast Track designation, are orphan drugs and what diseases the NCEs address from the Drugs@FDA Database (US Food and Drug Administration, 2021a). I verified whether an NCE indeed has the status of an orphan drug using the FDA Orphan Drug Product Designation database (US Food and Drug Administration, 2021b). I determined whether NCEs approved between 2008 and 2013 are first-in-class drugs based on classifications by Eder et al. (2014). I verified first-in-class classifications by Eder et al. (2014) using drug database searches, such as DrugBank (DrugBank, 2021) and internet searches. I identified whether NCEs approved in 2013, 2014 and 2015 are first-in-class drugs using FDA annual reports (US Food and Drug Administration, 2013, 2014, 2015).

I obtained the trade name, drug name, approval year and FDA applicant of all FDA-approved NBEs between 2008 and 2015 (sample 1) from FDA archives from the Center for Biologics Evaluation and Research (CBER) (US Food and Drug Administration, 2010). I classified all NBEs as biologics. I assessed whether the NBEs obtained priority review designation and Fast Track designation, whether the NBE is an orphan drug and first-in-class drug and what disease the NBE addresses using drug database searches, such as DrugBank (DrugBank, 2021) and internet searches.

I determined the US prevalence corresponding to the diseases the NMEs address using Institute for Health Metrics and Evaluation data and the Global Health Data Exchange tool (GHDx, 2021) and internet searches. I determined the height-of-peak sales and time-to-peak sales per drug based on financial statements (such as SEC 10-K filings), industry reports and corporate websites. I adjusted the height-of-peak sales for inflation using the US Biomedical Research and Development Index (National Institutes of Health, 2021). As a result, all sales were in 2021 US dollars.

For every NME (sample 1), I investigated which companies were involved in clinical trials phases I, II and III using the Clinical Trials database of the US National Library of Medicine (US National Library of Medicine, 2021). I identified which company obtained FDA approval from the CDER Drugs@FDA database (US Food and Drug Administration, 2021a) and CBER archives (US Food and Drug Administration, 2010). I identified the company that commercialised the NME at the time of peak sales as the marketer. I supplemented and verified the list of which companies were involved in which stage of development and commercialisation using corporate websites, news articles, scientific publications of clinical trials results, FDA and EMA documents and internet searches. For all FDA-approved NDAs excluding NMEs and already marketed drugs (sample 2), I identified the company responsible for obtaining FDA approval using the CDER Drugs@FDA database (US Food and Drug Administration, 2021a). I assessed whether the FDA approvals in sample 2 corresponded to a small molecule or biologic based on the molecular structure, mechanism of action and manufacturing method. I obtained information to synthesise primary data on organisational characteristics from corporate websites, financial statements, the Clinical Trials database of the US National Library of Medicine (US National Library of Medicine, 2021), scientific publications and news articles.

3.5 Sales calculation

Current studies have generally estimated the commercial success at the project level in the pharmaceutical industry using peak sales, i.e. the maximum sales a drug reaches in a year. The rationale behind using peak sales is that it allows for easy and fast estimation of financial performance. However, the reliability of using peak sales as an estimate of commercial success is questionable. According to Fischer et al. (2010), peak sales only explain 59.6% of the

variance in cumulative sales. In contrast, the height of the peak sales and the time required to reach the peak sales combined explain 96.5% of the variance in the cumulative sales. Hence, a combination of height-of-peak sales and time-to-peak sales is a good predictor for estimating cumulative sales. Therefore, I used the height-of-peak sales and time-to-peak sales in combination to calculate the cumulative sales of a drug. To accommodate the different moments that drugs were launched, I calculated the cumulative sales from when the drug was launched to the time-of-peak sales.

I assumed that the sales of a drug from market launch to time-to-peak sales follow an S-curve.[3] Therefore, I estimated the product life cycle of a drug using a logistic function (equation 3.1), where α is the maximum point of the curve (the height-of-peak sales in US dollars), β is the time-to-peak sales in years, and t is the time in years. Further assumptions of the sales calculation were that the logistic curve is symmetric ($f(t = \frac{1}{2}\,\beta) = \frac{1}{2}\,\alpha$) and the logistic growth rate is 1. Figure 3.2 shows an example of a product life cycle of a drug from market launch to time-to-peak sales using the logistic function (equation 3.1), where α = \$463 m and $\beta = 8$ years.

$$f(t) = \frac{\alpha}{1 + e^{-t+\frac{1}{2}\beta}} \tag{3.1}$$

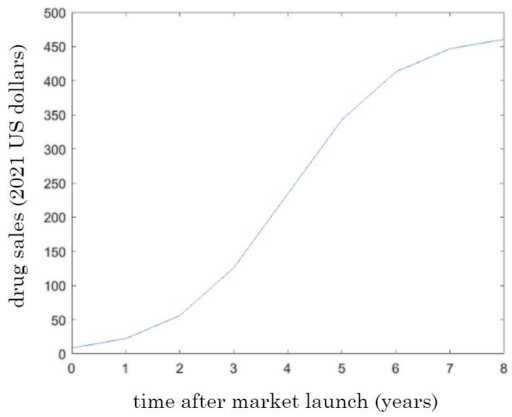

Figure 3.2: **An example representation of the logistic growth of drug sales over time.** In this example, the height-of-peak sales is \$463 m, and the time-to-peak sales is 8 years.

I calculated the cumulative sales from market launch to time-of-peak sales by integrating equation 3.1 from $t = 0$ until $t = \beta$ (= time-to-peak sales) (equation 3.2) using MATLAB.

[3]Before using the logistic growth curve as an estimation of the product life cycle from market launch to time-to-peak sales, I attempted to use of the alpha-distribution model for product life cycle modelling based on the advice of Prof. Marc Fischer (Petrescu, 2009). However, this model revealed to be not suitable for this analysis.

$$\int_0^{\beta} \frac{\alpha}{1 + e^{-t+\frac{1}{2}\beta}} dt \tag{3.2}$$

3.6 Statistical modelling

I used IBM SPSS Statistics 25 for statistical modelling. Depending on the types and distributions of the variables, I performed different kinds of statistical tests for hypothesis testing (Table 3.1).

Table 3.1: **Statistical tests used to test the hypotheses under investigation in this thesis, including independent variables, dependent variables and controlling variables.**

Hypothesis	**Indepdenent variable (type)**	**Depdenent variable (type)**	**Controlling variable (type)**	**Statistical test**
1.1	organisational characteristics (continuous)	*Cumulative sales* (continuous)	*Small molecule or biologic* (dichotomous)	multiple ordinary least squares regression with bootstrapping
1.2	organisational characteristics (continuous)	*Blockbusters* (continuous)	*Small molecule or biologic* (dichotomous)	multiple binary logistic regression
2	organisational characteristics (continuous)	*First-in-class drugs* (dichotomous)	*Small molecule or biologic* (dichotomous)	multiple binary logistic regression
3	organisational characteristics (continuous)	*Standard or priority review* (dichotomous)	*Small molecule or biologic* (dichotomous)	multiple binary logistic regression
4	organisational characteristics (continuous)	*Fast Track* (dichotomous)	*Small molecule or biologic* (dichotomous)	multiple binary logistic regression
5	organisational characteristics (continuous)	*Patient population* (continuous)	*Small molecule or biologic* (dichotomous)	multiple ordinary least squares regression with bootstrapping
6	organisational characteristics (continuous)	*Orphan drugs* (dichotomous)	*Small molecule or biologic* (dichotomous)	multiple binary logistic regression
7	organisational characteristics (continuous)	*Over-engineered drugs* (dichotomous)	*Small molecule or biologic* (dichotomous)	multiple binary logistic regression

I analysed the relationship between a continuous dependent and a continuous independent variable using an ordinary least squares (OLS) regression model. The residuals of all OLS

regression models in this study do not follow a normal or lognormal distribution. Given that bootstrapping does not assume normality of the residuals, I used a non-parametric bootstrapping approach to perform the OLS regressions. A bootstrapping approach can be used when the sample is a good representation of the population. The number of bootstrap samples was 10.000 (by default).

I used binary logistic regression models to establish relationships between the predictors and the probability of the dichotomous outcome. I tested the linearity assumption of binary logistic regression models using Box-Tidwell tests. A statistically significant interaction between the predictors and their logs (p-value smaller than or equal to 0.050) shows that the linearity assumption is violated. I tested the absence of multicollinearity assumption of multiple binary logistic regression models using variance inflation factor values. A variance inflation factor of below 10 shows that the multicollinearity assumption is not violated. I tested whether the model is a good fit using the Omnibus test for each binary logistic regression model. A p-value for the Omnibus test X^2 statistic smaller than or equal to 0.050 shows that the model is a significantly better fit than the null model. I tested the goodness-of-fit using the Hosmer and Lemeshow test. A p-value of the Hosmer and Lemeshow X^2 statistic greater than 0.050 shows that the observed and predicted probabilities do not significantly differ. I used the minimum sample size rule of thumb $n = 10k/p$ (where n = minimum sample size, k = number of predictors and p = frequency of the limiting sample) to assess whether the multiple binary logistic regression models in this thesis have adequate statistical power (Peduzzi et al., 1997). I validated that the sample size allowed for sufficient statistical power for all multiple binary logistic regression models.

To further analyse some of the established relationships (section 5.1), I performed mediation analyses to distinguish between direct and indirect effects of multiple independent variables on the dependent variable. I performed mediation analyses using the Hayes PROCESS version 3.5 macro modelling tool for SPSS (Hayes, 2017). Model 4 of the Hayes PROCESS macro modelling tool (the mediation model) assumes a continuous or dichotomous independent variable, continuous mediators and a continuous or dichotomous dependent variable. Depending on whether the dependent variable is continuous or dichotomous, the tool performs a multiple OLS regression or a multiple binary logistic regression, respectively. The tool determines the effect sizes of the direct and indirect effects using bootstrapping. The number of bootstrap samples was 5.000 (by default).

Chapter 4

Descriptive statistics

4.1 Descriptive statistics independent variables

Between 2008 and 2015, 239 companies developed and commercialised 306 new drugs (sample 1). In addition, 202 companies obtained FDA approval for 531 NDAs (sample 2). An overlap of 66 companies exists between sample 1 and sample 2. I assessed every company in the samples based on four organisational characteristics: age, origin, position in the value chain and specialisation. For each characteristic of every company, I analysed whether it resembled a pharmaceutical or a biotechnology company more (see section 3.2). Figure 4.1 shows the percentages of the firms in samples 1 and 2 with organisational characteristics that resembled a biotechnology firm rather than a pharmaceutical firm.

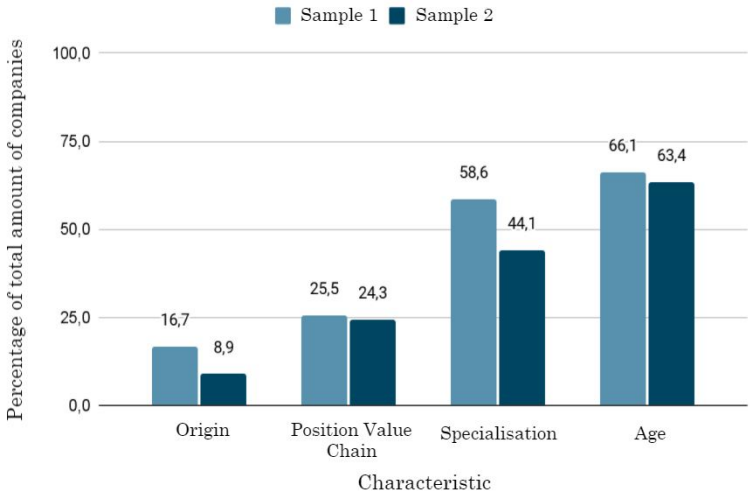

Figure 4.1: **Representation of the biotechnological organisational characteristics of firms responsible for developing and commercialising the new drug applications in samples 1 and 2.** A total of 239 firms were responsible for developing and commercialising the 306 new drugs in sample 1 and a total of 202 firms were responsible for gaining FDA approval for the 531 new drug applications in sample 2.

For every organisational characteristic, a larger percentage of firms resembled a biotechnology firm in sample 1 than in sample 2 (Figure 4.1). The large percentage of firms resembling a biotechnology firm in sample 1 compared to sample 2 indicates that biotechnology firms were more involved in developing new drugs than in developing new drug applications. In addition, a smaller percentage of firms resembled a pharmaceutical firm in sample 1 than in sample 2 considering every organisational characteristic. The smaller percentage indicates that pharmaceutical firms were relatively more involved in developing new drug applications than new drugs. More firms in samples 1 and 2 were incorporated after 1976 (66.1% and 63.4%, respectively) than before 1976 (33.9% and 36.6%, respectively). A minority of the firms in samples 1 and 2 focused on drug discovery and early development (25.5% and 24.3%, respectively). Instead, many firms in samples 1 and 2 focused also or exclusively on downstream activities (74.5% and 75.7%, respectively). A tiny fraction of the companies in samples 1 and 2 originated from universities, public research institutes and hospitals (16.7% and 8.9%, respectively). The percentage of firms with an academic origin in sample 1 (new drugs) (16.7%) was almost twice as high as in sample 2 (new drug applications) (8.9%). In samples 1 and 2, 58.6% and 44.1% of the firms were specialised, while 41.4% and 55.9% of the firms had a broad R&D project portfolio, respectively. The percentage of specialised companies was significantly higher in sample 1 (58.6%) than in sample 2 (44.1%). The relatively large percentage of firms with an academic origin and with a specialised R&D portfolio in sample 1 compared to sample 2 provides a first indication that these organisational characteristics may be important for developing new drugs.

Table 4.1 shows the descriptive statistics of the variables of the four organisational characteristics in each of the five stages of drug development and commercialisation of new drugs (sample 1).

Table 4.1: **Descriptive statistics of the four organisational characteristics in the five stages of development and commercialisation of companies in sample 1.**

		Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	N	296	297	294	300	301
	Min	0.00	0.00	0.00	0.00	0.00
	Max	1.00	1.00	1.00	1.00	1.00
	Mean	0.4479	0.4588	0.4450	0.4950	0.3738
	Std. Deviation	0.47334	0.4721	0.4610	0.5000	0.4733
Origin	N	296	297	294	300	301
	Min	0.00	0.00	0.00	0.00	0.00
	Max	1.00	1.00	1.00	1.00	1.00
	Mean	0.1757	0.1860	0.1751	0.2083	0.1213
	Std. Deviation	0.36297	0.3704	0.3604	0.4058	0.3179
Position Value Chain	N	296	297	294	300	301
	Min	0.00	0.00	0.00	0.00	0.00
	Max	1.00	1.00	1.00	1.00	1.00
	Mean	0.1768	0.1697	0.1479	0.1162	0.0897
	Std. Deviation	0.3653	0.3541	0.3338	0.3676	0.2682
Specialisation	N	296	297	294	300	301
	Min	0.00	0.00	0.00	0.00	0.00
	Max	1.00	1.00	1.00	1.00	1.00
	Mean	0.4183	0.4200	0.4144	0.4217	0.3821
	Std. Deviation	0.4698	0.4697	0.4618	0.4938	0.4781

The mean values of the variable *Age* ranged between 0.3738 and 0.4950 (Table 4.1), which means that 37.38% to 49.50% of the new drugs were associated with firms incorporated after 1976. In addition, it means that 50.50% to 62.62% of the new drugs corresponded to firms incorporated before 1976. In the three phases of clinical development, slightly more new drugs corresponded to firms incorporated before 1976 (around 55%) than after 1976 (around 45%). A similar percentage of firms incorporated before and after 1976 obtained FDA approval for the new drugs. Significantly more firms incorporated before 1976 were involved in marketing (62.62%) than in clinical development and FDA application (45% and 50.50%, respectively).

For the variable *Origin*, the mean values ranged from 0.1213 to 0.2083 (Table 4.1), which means that 12.13% to 20.83% of the new drugs were related to firms that originate from universities, public research institutes and hospitals. Moreover, it means that 79.17% to 87.87% of the new drugs were associated with firms without an academic origin. In the three phases of clinical development, fewer new drugs corresponded to firms with an academic origin (around 12%) than without (around 88%). More firms with an academic origin were involved in obtaining FDA approval for new drugs (20.83%) than in their clinical development (around

18%). Significantly fewer firms with an academic origin were involved in the marketing of new drugs (12.13%) than in clinical development and FDA application (18% and 20.83%, respectively).

The mean values of the variable *Position Value Chain* ranged from 0.0897 to 0.1768 (Table 4.1), which means that 8.97% to 17.68% of the new drugs corresponded to firms focused on drug discovery and early development. Furthermore, it indicates that 82.32% to 91.03% of the new drugs were related to firms that additionally or exclusively focused on downstream activities. Unsurprisingly, the further in the process of drug development and commercialisation, the more new drugs corresponded to firms that additionally or exclusively focused on downstream activities rather than on drug discovery and early development.

For the variable *Specialisation*, the mean values ranged from 0.3821 to 0.4200 (Table 4.1), meaning that 38.21% to 42.00% of the new drugs were associated with firms specialised in particular therapeutic areas or platform technology. Moreover, it means that 58.00% to 61.79% of the new drugs corresponded to firms with a broad R&D portfolio. In the three clinical development phases and FDA application, around 42% of the new drugs were related to specialised companies and around 58% to companies with a broad R&D portfolio. Less specialised firms were involved in the marketing of new drugs (38.21%) than in clinical development and FDA application (around 42%).

Table 4.2 shows the descriptive statistics of the variables of the four organisational characteristics of firms responsible for the new drug applications in sample 2.

Table 4.2: **Descriptive statistics of each of the four organisational characteristics corresponding to the companies involved in obtaining FDA approval for the NDAs in sample 2.**

	N	**Frequency (percentage)**		**Min - Max**
		0	**1**	
Age	531	268 (50.5%)	263 (49.5%)	0.00 - 1.00
Origin	531	488 (91.9%)	43 (8.1%)	0.00 - 1.00
Position Value Chain	531	448 (84.4%)	83 (15.6%)	0.00 - 1.00
Specialisation	531	351 (66.1%)	180 (33.9%)	0.00 - 1.00

Similar amounts of new drug applications in sample 2 corresponded to firms incorporated before and after 1976 (Table 4.2). Of all new drug applications in sample 2, 50.5% corresponded to a company incorporated before 1976 and 49.5% after 1976. A small fraction of

the new drug applications in sample 2 was associated with firms that originated from universities, public research institutes and hospitals and that focused on drug discovery and early development (8.1% and 15.6%, respectively). A great majority of the new drug applications in sample 2 corresponded to firms that did not originate from universities, public research institutes and hospitals and that were not focused on drug discovery and early development (91.9% and 84.4%, respectively). More new drug applications in sample 2 corresponded to firms with a broad R&D portfolio (66.1%) than firms specialised in particular therapeutic areas or a platform technology (33.9%).

4.2 Descriptive statistics dependent variables

Table 4.3 shows the descriptive statistics of the continuous dependent variables. The mean value of the cumulative sales from market launch to time-to-peak sales was approximately \$3.33 ± 6.00 billion (in 2021 US dollars). The cumulative sales of new drugs approved between 2008 and 2015 ranged from \$0.49 million to \$43448.21 million. The wide range and large standard deviation of the variable *Cumulative sales* show that significant variability existed among the sales of the new drugs. The mean patient population was approximately 9.04 ± 19.76 million patients. The patient population of the newly approved drugs between 2008 and 2015 ranged from 20 patients to 131.02 million patients. Similarly, the wide range and large standard deviation of the variable *Patient population* shows that significant variability existed among the number of patients potentially treated by the new drugs.

Table 4.3: **Descriptive statistics of continuous dependent variables *Cumulative sales* and *Patient population*.** The unit of cumulative sales from market launch to time-to-peak sales is millions of inflation-adjusted dollars (2021 US dollars). The unit of the patient population is the number of patients.

	N		**Mean**	**Std. Deviation**	**Range**	**Minimum**	**Maximum**
	Valid	**Missing**					
Cumulative sales	253	53	3338.09	5997.99	43447.72	0.49	43448.21
Patient population	266	40	9044420.474	19763137.03	131015980	20	131016000

Table 4.4 presents the mean and standard deviation of the continuous dependent variables per year from 2008 to 2015. The inconsistency in the mean values and the large standard deviations of the variables *Cumulative sales* and *Patient population* confirm that large variability in obtained sales and potential patients existed among new drugs. However, no trends in the means of the variables were distinguished. In addition, the mean values of *Cumulative sales* and *Patient population* did not seem to move together.

Table 4.4: **Mean and standard deviation of the continuous dependent variables *Cumulative sales* and *Patient population* per year from 2008 to 2015.**

Year	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2008 - 2015**
Cumulative sales	2.47 b ± 3.40 b	2.72 b ± 7.60 b	5.12 b ± 5.83 b	4.03 b ± 7.88 b	3.44 b ± 6.82 b	4.34 b ± 5.70 b	3.90 b ± 6.34 b	1.90 b ± 3.08 b	3.33 b ± 6.00 b
Patient population	11.00 m ± 2.53 m	10.15 m ± 2.34 m	9.86 m ± 18.43 m	12.62 m ± 27.54 m	10.23 m ± 25.42 m	6.80 m ± 10.51 m	11.03 m ± 16.04 m	3.16 m ± 6.70 m	9.04 m ± 19.76 m

Table 4.5 and 4.6 present the descriptive statistics of the dichotomous dependent variables between 2008 and 2015 and per year from 2008 to 2015, respectively. Between 2008 and 2015, significantly more new drugs were biologics (38.9%) than new drug applications (3.0%) (Table 4.5). Almost all new drug applications were small molecules (97.0%), while 61.1% of the new drugs were small molecules. The number of new biologics per year remained stable (Table 4.6). A fair amount of new drugs obtained blockbuster status between 2008 and 2015 (24.8%) (Table 4.5). The number of blockbusters per year seems to be increasing (Table 4.6), which suggests that an increasing fraction of new drugs is reaching annual sales of more than $1 billion. A considerable share of new drugs approved between 2008 and 2015 obtained a priority review designation from the FDA (42.2%) and was first-in-class (34.3%) (Table 4.5). The number of new drugs that obtained a priority review designation rather than a standard review designation significantly increased between 2008 and 2015 (Table 4.6). In addition, the number of new first-in-class drugs increased remarkably. The increase in the fraction of new priority review drugs and first-in-class drugs can indicate that an increasing portion of the new drugs is medically important and innovative. A substantial amount of new drugs approved between 2008 and 2015 obtained Fast Track designation from the FDA (33.0%) and were orphan drugs (37.3%) (Table 4.5). Between 2008 and 2015, the number of new drugs that obtained Fast Track designation and were orphan drugs increased (Table 4.6). This increase suggests that an increasing share of new drugs address previously unmet medical needs and small niche markets.

Table 4.5: **Descriptive statistics of dichotomous dependent variables.**

Variable	**Frequency (percentage)**		**N (percentage)**	
	0	**1**	**Valid**	**Missing**
Small molecule or biologic sample 1	187 (61.1%)	119 (38.9%)	306 (100%)	0 (0%)
Small molecule or biologic sample 2	515 (97.0%)	16 (3.0%)	531 (100%)	0 (0%)
Blockbusters	230 (57.8%)	76 (24.8%)	253 (82.3%)	53 (17.3%)
Standard or priority review	176 (57.5%)	129 (42.2%)	305 (99.7%)	1 (0.3%)
First-in-class drugs	201 (65.7%)	105 (34.3%)	306 (100%)	0 (0%)
Fast Track	204 (66.7%)	101 (33.0%)	305 (99.7%)	1 (0.3%)
Orphan drugs	191 (62.4%)	114 (37.3%)	305 (99.7%)	1 (0.3%)
Over-engineered drugs	455 (77.9%)	129 (22.1%)	584 (100%)	0 (0%)

Table 4.6: **Descriptive statistics of dichotomous dependent variables per year from 2008 to 2015.**

Amount of a variable	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2008 - 2015**
Biologics sample 1 (% of total NMEs)	10 (37.0%)	14 (41.2%)	12 (44.4%)	12 (35.3%)	14 (31.8%)	12 (35.3%)	21 (42.9%)	24 (42.1%)	119 (38.9%)
Blockbusters (% of total)	5 (18.5%)	4 (11.8%)	9 (33.3%)	9 (26.5%)	9 (20.5%)	11 (32.4%)	15 (30.6%)	14 (24.6%)	76 (24.8%)
Priority review designations (% of total)	9 (33.3%)	11 (32.4%)	12 (44.4%)	15 (44.1%)	15 (34.1%)	10 (29.4%)	27 (55.1%)	28 (49.1%)	127 (41.5%)
First-in-class drugs (% of total NMEs)	3 (11.1%)	5 (14.7%)	11 (40.7%)	17 (50.0%)	17 (38.6%)	12 (35.3%)	19 (38.8%)	21 (36.8%)	105 (34.3%)
Fast Track designations (% of total)	6 (22.2%)	8 (23.5%)	9 (33.3%)	15 (44.1%)	17 (38.6%)	11 (32.4%)	18 (36.7%)	17 (29.8%)	101 (33.0%)
Orphan drugs (% of total)	9 (33.3%)	14 (41.2%)	8 (29.6%)	13 (38.2%)	14 (31.8%)	13 (38.2%)	21 (42.9%)	22 (38.6%)	114 (37.3%)

Chapter 5

Results

This chapter will present the results from hypothesis testing. Section 5.1 will consider the statistical-test results for answering research subquestion 1: *What is the contribution of biotechnology firms to pharmaceutical R&D productivity?* Section 5.2 will present the results of the hypothesis tests for addressing research subquestion 2: *Are biotechnology firms disrupting the pharmaceuticals market through new-market disruption?*

5.1 R&D productivity

This section will analyse the contribution of biotechnology firms to pharmaceutical R&D productivity (subquestion 1). The determinants of pharmaceutical R&D productivity under investigation in this study are commercial success, innovativeness and medical importance of new medicines. This section will present the results from testing whether firms with biotechnological organisational characteristics have more commercial success (hypothesis 1, section 5.1.1), are more innovative (hypothesis 2, section 5.1.2) and are more medically important (hypothesis 3, section 5.1.3).

5.1.1 Commercial success

5.1.1.1 Cumulative sales

First, I assessed whether new drugs of firms with biotechnological organisational characteristics are positively correlated with cumulative sales from market launch to time-to-peak sales (hypothesis 1.1). I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *Cumulative sales* (dependent variable) using multiple OLS regressions with bootstrapping. Additional controlling variables were *Patient population* and *Orphan drugs*. Additionally, I performed mediation analyses to distinguish between direct and indirect effects of individ-

ual organisational characteristics on *Cumulative sales*. Table 5.1 shows the multiple OLS regression results.

Table 5.1: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and drug sales.** The relationships were tested using OLS regressions with bootstrapping. One OLS regression was performed per organisational characteristic per stage of clinical development and commercialisation. In every OLS model, *Small molecule or biologic*, *Patient population* and *Orphan drugs* were controlling variables.

Characteristic	**Coefficients (sig.)**				
	Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	-786.662	-1004.332	-1815.593**	-1089.647	-1607.401*
(sig.)	(0.384)	(0.251)	(0.017)	(0.165)	(0.040)
Origin	485.824	34.706	110.358	385.402	-993.361
(sig.)	(0.695)	(0.977)	(0.918)	(0.678)	(0.241)
Position Value Chain	-571.426	-546.668	480.146	-87.848	-2720.730
(sig.)	(0.620)	(0.614)	(0.736)	(0.930)	(0.063)
Specialisation	-1954.644*	-1849.584*	-1672.967*	-1749.029*	-1845.776*
(sig.)	(0.023)	(0.023)	(0.045)	(0.028)	(0.014)

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

The results suggested that *Age* is negatively correlated with *Cumulative sales* for all stages of drug development and commercialisation (Table 5.1). Moreover, the results indicated that the negative correlations between *Age* and *Cumulative sales* are significant for phase III and marketing. A one-unit increase in the value of *Age* results in a decrease in the mean value of *Cumulative sales* of 1815.593 and 1607.401 million of inflation-adjusted 2021 US dollars for phase III and marketing, respectively. These results suggest that firms involved in phase III and marketing generate on average 1815.593 and 1607.401 million US dollars less from market launch to time-to-peak sales, respectively, when incorporated after instead of before 1976. The mediation analyses indicated that the total negative effect of *Age* on *Cumulative sales* contains a significant direct negative effect.[1] Furthermore, it contains a significant indirect negative effect via *Specialisation*. These findings indicate that firms incorporated after 1976 generate significantly less cumulative drug sales from market launch to time-to-peak sales than companies incorporated before 1976.

For all stages of drug development and commercialisation, the results suggested that *Specialisation* is negatively correlated with *Cumulative sales* (Table 5.1). Additionally, the analyses

[1] Mediator variables were *Origin*, *Position Value Chain* and *Specialisation*.

indicated a significant relationship between *Specialisation* and *Cumulative sales* in all five stages of development and commercialisation. A one-unit increase in the value of *Specialisation* results in a decrease in the mean value of *Cumulative sales* of 1954.644, 1849.584, 1672.967, 1749.029 and 1845.776 million of inflation-adjusted 2021 US dollars for phases I, II and III, FDA application and marketing, respectively. These results suggest that firms involved in phases I, II and III, FDA application and marketing generate on average 1954.644, 1849.584, 1672.967, 1749.029 and 1845.776 million US dollars less from market launch to time-to-peak sales, respectively, when having a specialised rather than a generalised R&D portfolio. The mediation analyses indicated that *Specialisation* is directly negatively correlated with *Cumulative sales* and significantly indirectly via *Age*.[2] These findings suggest that specialised companies generate significantly less cumulative drug sales from market launch to time-to-peak sales than firms with broad R&D portfolios.

The results of the multiple binary logistic regression and mediation analyses suggested that the organisational characteristics *Origin* and *Position Value Chain* are not significantly directly correlated with *Cumulative sales* (Table 5.1). These results indicate that the origin and position in the value chain of a drug-developing company do not affect a firm's ability to generate drug sales.

5.1.1.2 Blockbusters

Second, I assessed whether new drugs of firms with biotechnological organisational characteristics rather than pharmaceutical organisational characteristics are more likely to be blockbusters (hypothesis 1.2). I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *Blockbusters* (dependent variable) using multiple binary logistic regressions. Additional controlling variables were *Patient population* and *Orphan drugs*. Additionally, I performed mediation analyses to distinguish between direct and indirect effects of individual organisational characteristics on *Blockbusters*. Table 5.2 shows the multiple binary logistic regression results.

[2]Mediator variables were *Age*, *Origin* and *Position Value Chain*.

Table 5.2: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and the development of blockbusters.** The relationships were testing using multiple binary logistic regressions. One multiple binary logistic regression was performed per organisational characteristic per stage of drug development and commercialisation. In every model, *Small molecule or biologic* was the controlling variable. A cell was coloured red when the linearity or multicollinearity assumption was violated, Omnibus test $p \leq 0.050$ or Hosmer and Lemeshow test $p > 0.050$. A cell was coloured green when the model fulfilled all four conditions.

Coefficient	**Stages of drug development and commercialisation**				
	Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	-0.168	-0.158	-0.490	-0.462	-0.798*
(sig.)	(0.611)	(0.624)	(0.153)	(0.121)	(0.018)
Origin	0.532	0.449	0.425	0.349	-0.146
(sig.)	(0.114)	(0.248)	(0.285)	(0.318)	(0.745)
Position Value Chain	-0.155	-0.116	-0.035	0.040	-0.694
(sig.)	(0.720)	(0.786)	(0.938)	(0.919)	(0.252)
Specialisation	-0.784*	-0.695*	-0.858*	-0.633*	-0.869*
(sig.)	(0.010)	(0.033)	(0.012)	(0.039)	(0.009)

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

The results suggested that *Age* is significantly negatively correlated with *Blockbusters* for the marketing stage (Table 5.2). The results of the remaining *Age* and *Blockbusters* models cannot be interpreted reliably. The odds ratio indicated that when the the score of *Age* of marketers increases by 1[3], the likelihood of developing a blockbuster decreases 2.222 times. This result suggests that firms incorporated after 1976 are 2.222 times less likely to market a blockbuster than firms incorporated before 1976. The results from mediation analyses indicated that the negative relationship between *Age* and *Blockbusters* consists of a significant negative direct effect and a significant negative indirect effect via *Specialisation*.[4] These findings indicate that firms incorporated after 1976 are significantly less likely to develop blockbusters than firms incorporated before 1976.

None of the models with *Origin* and *Position Value Chain* as independent variables and *Blockbusters* as the dependent variable can be interpreted reliably (Table 5.2). The models do not represent a significantly better fit than the null model. In addition, the null hypotheses that the *Origin* and *Position Value Chain* coefficients are not zero are not rejected. Therefore,

[3] An increase in the score of a variable of an organisational characteristic by 1 (from 0 to 1) means that the organisational characteristic changes from pharmaceutical (score = 0) to biotechnological (score = 1).

[4] Mediator variables were *Origin*, *Position Value Chain* and *Specialisation*.

the analyses did not establish relationships between the origin and position in the value chain of drug-developing companies and the probability of developing a blockbuster. The absence of these relationships suggests that the origin and position in the value chain of drug-developing companies do not affect a firm's ability to develop blockbusters.

The results indicated that *Specialisation* and *Blockbusters* are significantly negatively correlated for all stages of drug development and commercialisation (Table 5.2). Nevertheless, only the correlations for phase III, FDA application and marketing can be interpreted reliably. The odds ratios suggested that when the scores of *Specialisation* for phase III, FDA application and marketing decrease by 1, the likelihood that a blockbuster is developed increases 2.358, 1.883 and 2.387 times, respectively. These results suggest that firms involved in phase III, FDA application and marketing are 2.358, 1.883 and 2.387 times less likely to develop or commercialise a blockbuster, respectively, when being specialised instead of having a broad R&D portfolio. The results from mediation analyses indicated that *Specialisation* is directly negatively significantly related to *Blockbusters* and indirectly significantly negatively associated with blockbusters via *Age*.[5] These findings indicate that specialised firms are significantly less likely to develop blockbusters than firms with a broad R&D portfolio.

5.1.1.3 Conclusion

From testing hypothesis 1.1, I concluded that firms with biotechnological organisational characteristics do not generate more cumulative sales from market launch to time-to-peak sales than firms with pharmaceutical organisational characteristics (Table 5.3). Furthermore, based on the results of testing hypothesis 1.2, I concluded that firms with biotechnological organisational characteristics rather than pharmaceutical firms are not more likely to develop blockbusters. Therefore, I concluded that firms with biotechnological organisational characteristics do not have more commercial success than firms with pharmaceutical organisational characteristics. Instead, the results suggest that firms with pharmaceutical organisational characteristics (incorporated before 1976 and with a broad R&D portfolio) even have relatively more commercial success. Hence, hypothesis 1 was rejected.

[5] Mediator variables were *Age*, *Origin* and *Position Value Chain*.

Table 5.3: **Conclusion hypothesis 1.**

Hypothesis	**Not rejected (+) or rejected (-)**			
	Age	**Origin**	**Position Value Chain**	**Speciali -sation**
H1: Firms with biotechnological organisational characteristics have more commercial success than firms with pharmaceutical organisational characteristics.	**-**	**-**	**-**	**-**
H1.1: Firms with biotechnological organisational characteristics generate more cumulative sales from market launch to time-to-peak sales than firms with pharmaceutical organisational characteristics.	-	-	-	-
H1.2: Firms with biotechnological organisational characteristics have a higher probability of developing blockbusters than firms with pharmaceutical organisational characteristics.	-	-	-	-

5.1.2 Innovative medicines

Besides commercial success, I estimated pharmaceutical R&D productivity based on the development of innovative drugs. I assessed whether new drugs of firms with biotechnological organisational characteristics rather than pharmaceutical organisational characteristics are more likely to be innovative (hypothesis 2). I determined the innovativeness of a new drug based on whether a drug was first in class. I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *First-in-class drugs* (dependent variable) using multiple binary logistic regressions. Additionally, I performed mediation analyses to distinguish between direct and indirect effects of individual organisational characteristics on *First-in-class drugs*. Table 5.4 shows the multiple binary logistic regression results.

Table 5.4: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and the development of innovative medicines.** The relationships were testing using multiple binary logistic regressions. One multiple binary logistic regression was performed per organisational characteristic per stage of drug development and commercialisation. In every model, *Small molecule or biologic* was the controlling variable. A cell was coloured red when the linearity or multicollinearity assumption was violated, Omnibus test $p \leq 0.050$ or Hosmer and Lemeshow test $p > 0.050$. A cell was coloured green when the model fulfilled all four conditions.

Coefficient	**Stages of drug development and commercialisation**				
	Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	0.643*	0.711**	0.408	0.318	0.663**
(sig.)	(0.015)	(0.007)	(0.132)	(0.198)	(0.010)
Origin	0.838*	0.858**	0.884**	0.669*	0.361
(sig.)	(0.012)	(0.008)	(0.009)	(0.023)	(0.334)
Position Value Chain	0.826*	0.981**	0.958**	0.717*	0.262
(sig.)	(0.014)	(0.005)	(0.009)	(0.030)	(0.563)
Specialisation	-0.430	-0.336	-0.392	-0.378	-0.362
(sig.)	(0.094)	(0.208)	(0.153)	(0.136)	(0.166)

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

The results suggested that positive correlations exist between *Age* and *First-in-class drugs* for all stages of drug development and commercialisation (Table 5.4). Nevertheless, only the correlations for phase I, phase II and marketing are significant. The odds ratios indicated that when the scores of *Age* for phase I, phase II and marketing increase by 1, the likelihood that a drug is a first-in-class drug increases 1.901, 2.036 and 1.942 times, respectively. These results suggest that firms involved in phase I, phase II and marketing of a new drug are 1.901, 2.036 and 1.942 times more likely to develop or commercialise innovative drugs, respectively, when incorporated after 1976 instead of before 1976. The mediation analyses indicated that the positive total effect of *Age* on *First-in-class drugs* contains a significant positive direct effect.[6] Moreover, it contains a significant positive indirect effect via *Origin* and a significant negative indirect effect via *Specialisation*. These findings indicate that companies incorporated after 1976 have a higher probability of developing innovative drugs than firms incorporated before 1976.

For all stages of drug development and commercialisation, *Origin* and *First-in-class drugs* are positively correlated (Table 5.4). However, the correlations are significant only for phase I,

[6]Mediator variables were *Origin*, *Position Value Chain* and *Specialisation*.

phase II, phase III and FDA application. The model with *Origin* as the independent variable and *First-in-class drugs* as the dependent variable for phase II can be reliably interpreted despite the violation of the linearity assumption. The statistical power of this model was sufficiently large that the outcome is robust to violations of the linearity assumption. The odds ratios indicated that when the scores of *Origin* for phase I, phase II, phase III, and FDA application increase by 1, the likelihood that a drug is a first-in-class drug increases 2.311, 2.359, 2.421 and 1.952 times, respectively. These results suggest that firms involved in phases I, II and III and FDA application are 2.311, 2.359, 2.421 and 1.952 times more likely to develop innovative drugs when being spun out of academia instead of not having an academic origin. The results from mediation analyses indicated that the total positive effect of *Origin* on *First-in-class drugs* contains a significant positive direct effect.[7] Moreover, it contains a significant positive indirect via *Age* and a significant negative effect via *Specialisation*. These findings suggest that firms that originated from universities, public research institutes and hospitals have a higher probability of developing innovative drugs than firms that did not spin out of academia.

For all stages of drug development and commercialisation, the results indicated that *Position Value Chain* and *First-in-class drugs* are positively correlated (Table 5.4). However, only for phases II and III and FDA application, the coefficients of *Position Value Chain* are significant, and the models can be interpreted reliably. The odds ratios suggested that when the scores of *Position Value Chain* for phase II, phase III and FDA application increase by 1, the likelihood that a first-in-class drug is developed increases 2.667, 2.606 and 2.047 times, respectively. Nevertheless, the mediation analyses indicated that the total positive relationship between *Position Value Chain* and *First-in-class drugs* contains an insignificant direct effect.[8] Moreover, it contains a positive indirect effect via *Origin* and *Specialisation*. These findings suggest that the position in the value chain of a drug-developing firm does not affect the company's ability to develop innovative medicines.

The results indicated that *Specialisation* and *First-in-class drugs* are negatively correlated in all stages of drug development and commercialisation (Table 5.4). While none of the coefficients of *Specialisation* is significant, the standard errors are sufficiently low to suggest that all *Specialisation* coefficients are negative. The results from mediation analyses suggested that the total insignificant negative effect of *Specialisation* on *First-in-class drugs* contains a significant negative direct effect.[9] Moreover, it contains significant positive indirect effects via *Age* and *Origin*. These findings indicate that firms with broad rather than specialised R&D portfolios are more likely to develop innovative drugs.

From testing hypothesis 2, I concluded that firms with the biotechnological organisational

[7] Mediator variables were *Age*, *Position Value Chain* and *Specialisation*.
[8] Mediator variables were *Age*, *Origin* and *Specialisation*.
[9] Mediator variables were *Age*, *Origin* and *Position Value Chain*.

characteristics of being incorporated after 1976 and being an academic spin-out are significantly more likely to develop innovative drugs (Table 5.5). This conclusion is in accordance with the expectation. In contrast, the biotechnological organisational characteristic of being focused on drug discovery and early development was not directly positively correlated with the probability of developing innovative drugs at the $p \leq 0.050$ level. Moreover, surprisingly, the results suggested that a significant direct positive correlation exists between the pharmaceutical organisational characteristic of having a broad R&D portfolio and the probability of developing innovative drugs. This finding is in contrast to the expectation that firms with the biotechnological organisational characteristic of a specialised R&D portfolio are more likely to develop innovative drugs.

Table 5.5: **Conclusion hypothesis 2.**

Hypothesis	**Not rejected (+) or rejected (-)**			
	Age	**Origin**	**Position Value Chain**	**Specialisation**
H2: Firms with biotechnological organisational characteristics have a higher probability of developing innovative drugs than firms with pharmaceutical organisational characteristics.	+	+	-	-

5.1.3 Medically-important drugs

The final determinant of R&D productivity investigated was the development of medically-important drugs. I assessed whether new drugs of firms with biotechnological organisational characteristics rather than pharmaceutical organisational characteristics are more likely to be medically important (hypothesis 3). I determined the medical importance of new drugs based on whether a drug obtained a priority review designation. I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *Standard or priority review* (dependent variable) using multiple binary logistic regressions. Additionally, I performed mediation analyses to distinguish between direct and indirect effects of individual organisational characteristics on *Standard or priority review*. Table 5.6 shows the multiple binary logistic regression results.

Table 5.6: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and the development of medically-important drugs.** The relationships were testing using multiple binary logistic regressions. One multiple binary logistic regression was performed per organisational characteristic per stage of drug development and commercialisation. In every model, *Small molecule or biologic* was the controlling variable. A cell was coloured red when the linearity or multicollinearity assumption was violated, Omnibus test $p \leq 0.050$ or Hosmer and Lemeshow test $p > 0.050$. A cell was coloured green when the model fulfilled all four conditions.

Coefficient	**Stages of drug development and commercialisation**				
	Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	0.826**	0.633*	0.646*	0.455	0.457
(sig.)	(0.001)	(0.012)	(0.013)	(0.054)	(0.067)
Origin	1.018**	0.867**	0.732*	0.827**	0.703
(sig.)	(0.003)	(0.008)	(0.028)	(0.005)	(0.057)
Position Value Chain	0.542	0.546	0.223	0.438	0.185
(sig.)	(0.097)	(0.096)	(0.532)	(0.171)	(0.670)
Specialisation	-0.207	-0.110	-0.126	-0.322	-0.371
(sig.)	(0.412)	(0.662)	(0.624)	(0.178)	(0.135)

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

The results suggested that positive correlations exist between *Age* and *Standard or priority review* for all stages of drug development and commercialisation (Table 5.6). Nevertheless, only for phase III of clinical development, the correlation is significant, and the model can be interpreted reliably. While the linearity assumption of the model for phase III is violated, the statistical power of this model is sufficiently large that the outcome is robust to violations of this assumption. The odds ratio indicated that when the score of *Age* for phase III increases by 1, the likelihood that a priority review drug is developed increases 1.908 times. This result indicates that firms involved in phase III are 1.908 times more likely to develop a medically-important drug when incorporated after 1976 instead of before. The mediation analyses suggested that the total positive effect of *Age* on *Standard or priority review* contains a significant positive direct effect.[10] Moreover, it contains a significant positive indirect effect via *Origin* and a significant negative indirect effect via *Specialisation*. These findings suggest that companies incorporated after 1976 are significantly more likely to develop medically-important drugs than firms incorporated before 1976.

For all stages of drug development and commercialisation, the results suggested that *Origin*

[10]Mediator variables were *Origin*, *Position Value Chain* and *Specialisation*.

and *Standard or priority review* are positively correlated (Table 5.6). However, only for phase I, phase II and FDA application, the correlations are significant, and the models can be interpreted. While the linearity assumption of the models for phases I and II are violated, the statistical power of these models is sufficiently large that the outcomes are robust to violations of this assumption. The odds ratios indicated that when the scores of *Origin* for phase I, phase II and FDA application increase by 1, the likelihood that a priority review drug is developed increases 2.767, 2.380 and 2.286 times, respectively. These results suggest that companies involved in phase I, phase II and FDA application are 2.767, 2.380 and 2.286 times more likely to develop or commercialise medically-important drugs, respectively, when having an academic origin. The mediation analyses suggested that the total positive effect of *Origin* on *Standard or priority review* contains a significant positive direct effect.[11] Moreover, it contains a significant positive indirect effect via *Age* and a significant negative indirect effect via *Specialisation*. These findings indicate that firms that originated from universities, public research institutes and hospitals are significantly more likely to develop medically-important drugs than firms that did not.

The results suggested that, for all stages of drug development and commercialisation, *Position Value Chain* and *Standard or priority review* are positively correlated, and *Specialisation* and *Standard or priority review* are negatively correlated (Table 5.6). However, none of the correlations is significant, and none of the models can be interpreted reliably because they do not represent a significantly better fit than the null models. Nevertheless, the mediation analyses indicated that the insignificant total effect of *Specialisation* on *Standard or priority review* contains a significant direct negative effect.[12] Moreover, it contains significant indirect positive effects via *Age* and *Origin*. In addition, the mediation analyses suggested no significant direct or indirect effect of *Position Value Chain* on *Standard or priority review* exists. These findings suggest that firms with a broad R&D portfolio are more likely to develop medically-important drugs. Furthermore, the findings suggest that the position in the value chain of a drug-developing company does not affect the firm's ability to develop medically-important drugs.

In accordance with the expectation, I concluded that firms with the biotechnological organisational characteristics of being incorporated after 1976 and being an academic spin-out are significantly more likely to develop medically-important drugs (Table 5.7). In contrast to the expectation, I concluded that the biotechnological organisational characteristic of being focused on drug discovery and early development does not directly affect the probability of developing medically-important drugs. Moreover, surprisingly, I concluded that firms with the pharmaceutical organisational characteristic of having a broad R&D portfolio are significantly more likely to develop medically-important drugs.

[11] Mediator variables were *Age*, *Position Value Chain* and *Specialisation*.
[12] Mediator variables were *Age*, *Origin* and *Position Value Chain*.

Table 5.7: **Conclusion hypothesis 3.**

Hypothesis	**Not rejected (+) or rejected (-)**			
	Age	**Origin**	**Position Value Chain**	**Specialisation**
H3: Firms with biotechnological organisational characteristics have a higher probability of developing medically-important drugs than firms with pharmaceutical organisational characteristics.	+	+	-	-

5.2 New-market disruption

This section will examine whether firms with biotechnological organisational characteristics are disrupting the pharmaceuticals market via new-market disruption (subquestion 2). The elements of new-market disruption under investigation are the targeting of unserved customers in small niche markets by entrants and the targeting of demanding customers and over-engineering of drugs by incumbents. This section will present the results from testing whether firms with biotechnological organisational characteristics target more unserved customers (hypothesis 4, section 5.2.1) and more niche markets (hypothesis 6, section 5.2.3). Additionally, it will present whether firms with pharmaceutical organisational characteristics target more demanding customers (hypothesis 5, section 5.2.2) and develop more over-engineered drugs (hypothesis 7, section 5.2.4).

5.2.1 New-market development

The first element of new-market disruption investigated was the targeting of unserved customers by entrants. I assessed whether new drugs of firms with biotechnological organisational characteristics rather than pharmaceutical organisational characteristics were targeted at unserved customers by addressing unmet medical needs (hypothesis 4). I determined whether a drug was directed at unserved customers based on whether the drug obtained a Fast Track designation from the FDA. I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *Fast Track* (dependent variable) using multiple binary logistic regressions. Table 5.8 shows the multiple binary logistic regression results.

Table 5.8: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and the targeting of unserved customers.** The relationships were testing using multiple binary logistic regressions. One multiple binary logistic regression was performed per organisational characteristic per stage of drug development and commercialisation. In every model, *Small molecule or biologic* was the controlling variable. A cell was coloured red when the linearity or multicollinearity assumption was violated, Omnibus test $p \leq 0.050$ or Hosmer and Lemeshow test $p > 0.050$. A cell was coloured green when the model fulfilled all four conditions.

Coefficient	**Stages of drug development and commercialisation**				
	Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	0.472	0.339	0.391	0.554*	0.399
(sig.)	(0.074)	(0.199)	(0.149)	(0.027)	(0.125)
Origin	0.960**	0.740*	0.624	0.446	0.491
(sig.)	(0.005)	(0.026)	(0.068)	(0.136)	(0.193)
Position Value Chain	0.831*	0.685*	0.431	0.516	0.540
(sig.)	(0.012)	(0.048)	(0.239)	(0.115)	(0.227)
Specialisation	-0.206	-0.172	-0.335	-0.234	-0.081
(sig.)	(0.439)	(0.517)	(0.220)	(0.352)	(0.755)

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

The results suggested that *Age* and *Fast Track* are positively correlated for all stages of drug development and commercialisation (Table 5.8). The positive correlation of *Age* and *Fast Track* suggests that companies incorporated after rather than before 1976 are more likely to develop drugs that address unmet medical needs and thereby target unserved customers. While, strictly, none of the models can be interpreted reliably, the model for FDA application only did not have a significantly better fit than the null model ($p = 0.053$). Combined with the results that *Age* and *Fast Track* are positively correlated, sufficient evidence exists not to reject the hypothesis that firms incorporated after 1976 are more likely to target unserved customers.

For all stages of drug development and commercialisation, the results suggested that *Origin* and *Fast Track* are positively correlated (Table 5.8). The positive correlations between *Origin* and *Fast Track* are significant for phases I and II. The odds ratios indicated that when the score of *Origin* of companies involved in phase I increases by 1, the likelihood that a drug that obtains a Fast Track designation is developed increases 2.611 times. This result indicates that companies involved in phase I are 2.611 times more likely to develop drugs for unserved customers when having an academic origin. While, strictly, the model for phase I is the

only model that can be interpreted reliably, the model for phase II only did not have a significantly better fit than the null model ($p = 0.058$). These findings suggest that firms originating from universities, public research institutes and hospitals are more likely to target unserved customers compared to firms without an academic origin.

The results suggested that positive correlations exist between *Position Value Chain* and *Fast Track* exist for all stages of drug development and commercialization (Table 5.8). While the correlations for phase I and phase II are significant, only the model for phase I can be interpreted reliably. The odds ratio indicated that when the score of *Position Value Chain* of companies involved in phase I increases by 1, the likelihood that a drug obtains Fast Track designation increases 2.295 times. This result suggests that firms involved in phase I are 2.295 times more likely to develop drugs targeted at unserved customers when focused on drug discovery and early development instead of additionally or exclusively on downstream activities. The findings indicate that firms focused on drug discovery and early development are more likely to target unserved customers than firms focused additionally or exclusively on downstream activities.

For all stages of drug development and commercialisation, the results suggested that *Specialisation* and *Fast Track* are negatively correlated (Table 5.8). However, none of the models can be interpreted reliably because no model represents a significantly better fit than the null model. Therefore, no relationships between the specialisation in particular therapeutic areas or technologies and the probability of developing a drug that obtains a Fast Track designation were established. The absent relationships suggest that the specialisation or generalisation of the R&D portfolio of drug-developing companies does not affect a firm's tendency to develop new markets.

From testing hypothesis 4, I concluded that firms with the biotechnological organisational characteristics of being incorporated after 1976, spun out of academia and focused on drug discovery and early development are more likely to develop drugs addressing unmet medical needs (Table 5.9). This finding is in accordance with the expectation that biotechnology firms (the entrants) target unserved customers. However, in contrast to the expectation, I concluded that the biotechnological organisational characteristic of being specialised does not affect the probability of targeting unserved customers.

Table 5.9: **Conclusion hypothesis 4.**

Hypothesis	**Not rejected (+) or rejected (-)**			
	Age	**Origin**	**Position Value Chain**	**Speciali -sation**
H4: Firms with biotechnological organisational characteristics have a higher probability of developing drugs that address unmet medical needs than firms with pharmaceutical organisational characteristics.	+	+	+	-

5.2.2 Targeting the most demanding customers

The second element of new-market disruption investigated was the targeting of the most demanding customers by incumbents. I determined whether the most demanding customer segment was targeted based on the size of the patient population of the diseases the drugs address. I assessed whether new drugs of firms with pharmaceutical organisational characteristics are positively correlated with the patient populations of the diseases the drugs address (hypothesis 5). I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *Patient population* (dependent variable) using multiple OLS regressions with bootstrapping. Table 5.10 shows the multiple OLS regression results.

Table 5.10: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and the patient population of diseases new drugs address.** The relationships were tested using OLS regressions with bootstrapping. One OLS regression was performed per organisational characteristic per stage of clinical development and commercialisation. In every OLS model, *Small molecule or biologic* was the controlling variable.

Variable	**Coefficients (in millions) (sig.)**				
	Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	-8.567** (0.001)	-7.021* (0.023)	-8.111** (0.002)	-4.066 (0.094)	-3.437 (0.158)
Origin	-6.142** (0.005)	-5.432* (0.013)	-4.539 (0.053)	-6.148** (0.005)	-5.638** (0.010)
Position Value Chain	-4.890 (0.158)	-5.280 (0.120)	-3.610 (0.337)	-3.765 (0.242)	-1.711 (0.752)
Specialisation	-1.556 (0.539)	-3.034 (0.224)	-0.672 (0.821)	-2.890 (0.207)	-0.631 (0.827)

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

For all drug development and commercialisation stages, the results suggested that *Age* is negatively correlated with *Patient population* (Table 5.10). The correlations are significant for phases I, II and III of clinical development. A one-unit increase in the value of *Age* results in a decrease in the mean value of *Patient population* of 8.567, 7.021 and 8.111 million for phases I, II and III, respectively. These results suggest that firms involved in phases I, II and III target on average 8.567, 7.021 and 8.111 million potential customers less, respectively, when incorporated after instead of before 1976. These findings indicate that companies incorporated after 1976 target significantly smaller patient populations compared to firms incorporated before 1976.

The results suggested negative correlations between *Origin* and *Patient population* in all stages of clinical development and commercialisation (Table 5.10). The negative correlations are significant for phases I and II of clinical drug development, FDA application and marketing. A one-unit increase in the value of *Origin* results in a decrease in the mean value of *Patient population* of 6.142, 5.432, 6.148 and 5.638 million for phases I and II, FDA application and marketing, respectively. These results indicate that firms involved in phases I and II, FDA application and marketing target on average 6.142, 5.432, 6.148 and 5.638 million potential customers less, respectively, when originating from universities, public research institutes and hospitals. These findings suggest that firms with an academic origin significantly target smaller patient populations than firms without an academic origin.

For companies involved in all drug development and commercialisation stages, the results suggested that *Position Value Chain* and *Specialisation* were negatively correlated with *Patient population* (Table 5.10). The negative correlations between *Position Value Chain* and *Patient population* indicate that companies focused on drug discovery and early development target smaller patient populations than firms additionally or exclusively focused on downstream activities. Moreover, the negative correlations between *Specialisation* and *Patient population* suggest that firms focused on specific therapeutic areas or a technology platform target smaller patient populations than firms with a broad R&D portfolio. However, none of the correlations was significant. Therefore, being focused on drug discovery and early development and being specialised does not significantly affect a firm's tendency to target smaller patient populations.

From the results of the statistical tests (Table 5.10), I concluded that firms with the pharmaceutical organisational characteristics of being incorporated before 1976 and not having an academia origin target significantly larger patient populations (Table 5.11). This finding is in accordance with the expectation that pharmaceutical firms (the incumbents) target more demanding customers. In contrast to the expectation, I did not conclude that being additionally or exclusively focused on downstream activities and having a broad R&D portfolio are significantly correlated with the size of the patient population of the diseases the drugs

address.

Table 5.11: **Conclusion hypothesis 5.**

Hypothesis	**Not rejected (+) or rejected (-)**			
	Age	**Origin**	**Position Value Chain**	**Speciali -sation**
H5: Firms with pharmaceutical organisational characteristics are related to developing medicines for larger patient populations than firms with biotechnological organisational characteristics.	+	+	-	-

5.2.3 Targeting niche markets

The third element of new-market disruption investigated was the targeting of niche markets by entrants. I assessed whether new drugs of firms with biotechnological organisational characteristics rather than pharmaceutical organisational characteristics were targeted at niche markets (hypothesis 6). I determined whether a drug was directed at niche markets based on whether the drug was an orphan drug. I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *Orphan drugs* (dependent variable) using multiple binary logistic regressions. Table 5.12 shows the multiple binary logistic regression results.

Table 5.12: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and the targeting of niche markets.** The relationships were testing using multiple binary logistic regressions. One multiple binary logistic regression was performed per organisational characteristic per stage of drug development and commercialisation. In every model, *Small molecule or biologic* was the controlling variable. A cell was coloured red when the linearity or multicollinearity assumption was violated, Omnibus test $p \leq 0.050$ or Hosmer and Lemeshow test $p > 0.050$. A cell was coloured green when the model fulfilled all four conditions.

Coefficient	**Stages of drug development and commercialisation**				
	Phase I	**Phase II**	**Phase III**	**FDA Applicant**	**Marketer**
Age	0.665*	0.743**	0.733**	0.554*	0.579*
(sig.)	(0.011)	(0.005)	(0.006)	(0.032)	(0.023)
Origin	0.517	0.710*	0.467	0.610*	0.312
(sig.)	(0.120)	(0.029)	(0.164)	(0.037)	(0.400)
Position Value Chain	0.067	0.354	-0.317	0.189	-0.999
(sig.)	(0.845)	(0.311)	(0.414)	(0.568)	(0.065)
Specialisation	-0.420	-0.321	-0.365	-0.054	-0.126
(sig.)	(0.111)	(0.221)	(0.175)	(0.824)	(0.619)

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

For all stages of drug development and commercialisation, the results suggested that positive correlations exist between *Age* and *Orphan drugs* (Table 5.12). In addition, all correlations are significant. Nevertheless, only the models for phases II and III, FDA application and marketing can be interpreted reliably. The odds ratio indicated that when the scores of *Age* for phases II and III, FDA application and marketing increase by 1, the likelihood that an orphan drug is developed increases 2.101, 2.081, 1.688 and 1.784 times, respectively. These results suggest that firms involved in phases II and III, FDA application and marketing are 2.101, 2.081, 1.688 and 1.784 times more likely to target niche markets, respectively, when incorporated after rather than before 1976. These findings indicate that firms incorporated after 1976 are significantly more likely to target niche markets than companies incorporated before 1976.

The results suggested that *Origin* is positively correlated with *Orphan drugs* in all stages of drug development and commercialisation (Table 5.12). Moreover, the correlations for phase II and FDA application are significant. The odds ratios indicated that when the scores of *Origin* for phase II and FDA application increase by 1, the likelihood that an orphan drug is developed increases 2.034 and 1.840 times, respectively. These results suggest that firms involved in phase II and FDA application are 2.034 and 1.840 times more likely to target niche markets, respectively, when having an academic origin instead of not being originated from academia. These findings indicate that firms originating from universities, public research institutes and hospitals are significantly more likely to target niche markets than firms without an academic origin.

None of the models with *Position Value Chain* and *Specialisation* as independent variables and *Orphan drugs* as the dependent variable can be interpreted reliably (Table 5.12). Therefore, the analyses established no effects of *Position Value Chain* and *Specialisation* on *Orphan drugs*. The absent effects suggest that the position in the value chain and the specialisation of a drug-developing firm does not affect the company's tendency to target niche markets.

In accordance with the expectation, I concluded that firms with the biotechnological organisational characteristics of being incorporated after 1976 and having an academic origin are significantly more likely to target niche markets (Table 5.13). In contrast to the expectation, I did not conclude that being additionally or exclusively focused on downstream activities and having a broad R&D portfolio are significantly correlated with the probability of targeting niche markets.

Table 5.13: **Conclusion hypothesis 6.**

Hypothesis	**Not rejected (+) or rejected (-)**			
	Age	**Origin**	**Position Value Chain**	**Speciali -sation**
H6: Firms with biotechnological organisational characteristics have a higher probability of targeting small niche markets than firms with pharmaceutical organisational characteristics.	+	+	-	-

5.2.4 Over-engineered drugs

The final element of new-market disruption under investigation was the "over-engineering" of products by incumbents. I defined "over-engineered" as follows: When a company over-engineers a drug, the company further develops a drug in a way that does not represent a significant improvement compared to existing treatments. whether firms with pharmaceutical organisational characteristics rather than biotechnological organisational characteristics over-engineer drugs. I assessed whether NDAs of firms with pharmaceutical organisational characteristics rather than biotechnological organisational characteristics are more likely to be over-engineered (hypothesis 7). I analysed the correlations between several organisational characteristics (independent variables) in different stages of drug development and commercialisation and *Over-engineered drugs* (dependent variable) using multiple binary logistic regressions. For simplicity, I only considered the organisational characteristics of companies involved in obtaining FDA approval. Table 5.14 shows the multiple binary logistic regression results.

Table 5.14: **Relationship between organisational characteristics of biotechnology or pharmaceutical firms and the development of over-engineered medicines.** The relationships were testing using multiple binary logistic regressions. In every model, *Small molecule or biologic* was the controlling variable. In all models, the linearity and multicollinearity assumption were not violated, Omnibus test $p \geq 0.050$ or Hosmer and Lemeshow test $p < 0.050$.

Variable	*Age*	*Origin*	*Position Value Chain*	*Speciali -sation*
Coefficient	0.203	1.591*	0.484	0.055
(sig.)	(0.371)	0.000	(0.093)	(0.816)

* Correlation is significant at the $p \leq 0.01$ level (two-tailed)

The results suggested that all variables of the organisational characteristics are positively correlated with *Over-engineered drugs* (Table 5.14). These results suggest that firms with pharmaceutical organisational characteristics are more likely to develop over-engineered drugs.

However, only the correlation between *Origin* and *Over-engineered drugs* is significant. The odds ratio indicated that when the score of *Origin* increases by 1, the likelihood of developing an over-engineered drug decreases 4.908 times. This result suggests that firms are 4.908 times less likely to develop an over-engineered drug when originating from universities, public research institutes or hospitals instead of when not having an academic origin. These findings indicate that companies without an academic origin are significantly more likely to develop over-engineered medicines. In addition, the findings suggest that a firm's age, position in the value chain and specialisation of the R&D portfolio do not significantly affect its probability of developing over-engineered drugs.

Based on the results of the statistical tests (Table 5.14), I concluded that firms with the pharmaceutical organisational characteristic of not having an academic origin are significantly more likely to develop over-engineered medicines (Table 5.15). This finding supports the hypothesis that firms with pharmaceutical rather than biotechnological organisational characteristics develop more over-engineered medicines. Nevertheless, in contrast to the expectation, I did not conclude that being incorporated before 1976, being additionally or exclusively focused on downstream activities and having a broad R&D portfolio are significantly correlated with the probability of developing over-engineered drugs.

Table 5.15: **Conclusion hypothesis 7.**

Hypothesis	**Not rejected (+) or rejected (-)**			
	Age	**Origin**	**Position Value Chain**	**Speciali -sation**
H7: Firms with pharmaceutical organisational characteristics develop more over-engineered medicines than firms with biotechnological organisational characteristics.	-	+	-	-

Chapter 6

Discussion

This thesis aims to examine to what extent new-market disruption of the pharmaceuticals market by biotechnology firms contributes to reducing the pharmaceutical R&D productivity decline. In this chapter, first, I will discuss the results of the assessment of the current impact of biotechnology firms on pharmaceutical R&D productivity. I investigated the current impact by linking biotechnological organisational characteristics to the commercial success, innovativeness and medical importance of new medicines. Second, I will discuss the results of the assessment of the future impact of biotechnology firms on pharmaceutical R&D productivity. I assessed the future impact by examining whether biotechnology firms are disrupting the pharmaceuticals market through new-market disruption.

6.1 Impact of biotechnology firms on R&D productivity

The first research subquestion addressed was: *What is the contribution of biotechnology firms to pharmaceutical R&D productivity?* To answer this question, I analysed the relationships between several organisational characteristics and R&D productivity determinants. The investigated organisational characteristics included the origin, age, position in the value chain and specialisation of drug-developing firms. Furthermore, the R&D productivity determinants analysed were the commercial success, innovativeness and medical importance of new medicines. I will address each organisational characteristic consecutively.

First, I will discuss the effect of having an academic origin on R&D productivity determinants. The results suggest that firms originating from universities, research institutes and hospitals are significantly more likely to develop innovative and medically-important medicines than firms that are not academic spin-outs (section 5.1.2 and 5.1.3). This finding supports the idea that universities are key actors in the drug innovation system and highlights the importance of academic knowledge and technology transfer for drug innovation (Powell et al., 2002; Mehta, 2004; Melese et al., 2009; Kaitin, 2010; Kneller, 2010). This finding can be explained in at

least two ways. First, firms with an academic origin can be more likely to develop innovative and medically-important drugs because their aim is to commercialise cutting-edge technology and science. Second, the scientists of academic spin-outs generally have specific relevant knowledge and enjoy much autonomy, which can be conducive to innovation (Pisano, 2006b; Garnier, 2008). In contrast to the innovativeness and medical importance of new drugs, the current study indicates that drugs of firms with an academic origin are not significantly more likely to be commercially successful (section 5.1.1). This finding is consistent with a case study of Israelian university biotechnology spin-outs (Kaufmann et al., 2003). The absent significant effect of an academic origin on commercial success can be explained by the innovative edge of academic spin-outs being counteracted by a lack of commercial experience.

Second, I will discuss the relationship between a firm's age and R&D productivity determinants. The results suggest that drugs of firms incorporated after rather than before 1976 are significantly less successful commercially (section 5.1.1). This finding is consistent with those in a study by Cha and Yu (2014), which have highlighted the importance of previous commercial experience in a drug market for gaining market share. Several explanations for the comparative advantage of being relatively old for developing commercially-successful drugs exist. One possible explanation is that established firms are better at commercially exploiting new technological opportunities than entrants due to the established firms' absorptive capacity and accumulated knowledge (Cohen & Levinthal, 1990). Another possible explanation is that new biotechnologies are not necessarily competence-destroying. Established firms continue to enjoy comparative advantages from their accumulated libraries of drug candidates and targets, former discovery and development methodologies and revenues from previous products (Malerba & Orsenigo, 2015).

In contrast to the commercial success of new drugs, this study indicates that drugs of firms incorporated after 1976 are significantly more likely to be innovative and medically important (section 5.1.2 and 5.1.3). These results align with those of Balasubramanian and Lee (2008), which have shown that the quality of R&D output in the pharmaceutical industry (measured in terms of patent quality) strongly falls with firm age. The significantly better odds of developing innovative and medically-important medicines of firms incorporated after 1976 can be explained in several ways. First, relatively new firms can develop significantly more innovative and medically-important medicines than established firms because new firms have better access to cutting-edge science and technology from academia (Pisano, 2006b).[1] Second, new firms can develop more innovative and medically-important drugs than established firms because they are less hampered by organisational inertia and investments in specialised assets (Abernathy & Utterback, 1978). Third, new firms can be more likely to develop innovative and medically-important medicines because they are less worried about cannibalising their

[1] This explanation is empirically supported by this study's finding that the academic origin of new firms partially significantly explains their better odds of developing innovative and medically-important medicines.

products than established companies (Henderson & Clark, 1990).

Third, I will discuss the effect of a firm's position in the value chain on determinants of R&D productivity. The results suggest that a firm's position in the value chain does not directly affect the probability of developing innovative, medically-important and commercially-successful drugs (section 5.1). This finding is significant because it suggests that focusing on innovative activities as a core competency does not likely improve the new drug's innovativeness, medical importance, and commercial success. Additionally, it contradicts the common strategic advice for biotechnology firms to focus on drug discovery and development and for pharmaceutical firms to focus on downstream activities, such as marketing. Finally, the absence of a relationship between the position in the value chain and the determinants of R&D productivity can point to inefficiencies of the current division of innovative labour. However, the finding cannot be compared to previous studies. The present study represents the first empirical study on the presence of a comparative advantage of being focused on drug discovery and early development with respect to R&D productivity performance.

Finally, I will address the relationship between the specialisation or generalisation of the R&D portfolio and the R&D productivity performance. The present study indicates that being specialised in a particular platform technology or therapeutic areas impedes developing commercially successful, innovative and medically-important new medicines (section 5.1). This finding indicates that economies of scope play an important role in developing and commercialising new drugs, which is in line with findings of previous studies (Henderson & Cockburn, 1996; Cockburn & Henderson, 2001). Being specialised can negatively affect a firm's ability to develop commercially-successful, innovative and medically-important drugs because an emphasis on knowledge depth can come at the cost of knowledge breadth. Knowledge breadth is important for the integration of different disciplines, which is conducive to innovation and the recognition of the commercial potential of new science and technology.

The finding that specialised firms have worse odds of developing commercially-successful, innovative, and medically-important drugs is important from an organisational strategy perspective. It does not support the commonly held view that it is advantageous for a firm to focus on specific therapeutic areas. This finding implies that it is beneficial for pharmaceutical firms to maintain a broad, diversified R&D project portfolio. For biotechnology firms, the implications are more complicated. The development of diverse capabilities in-house is not financially feasible for a resource-constrained biotechnology firm, and knowledge-sharing in horizontal inter-firm collaborations is generally limited to protect tacit assets. Therefore, it is recommended for specialised biotechnology firms to gain access to a diverse pool of shared knowledge and establish intimate long-term relationships via venture philanthropy.

In conclusion, the young age and academic origin of biotechnology firms enhance their ability to develop innovative and medically-important drugs, but being specialised limits this ability.

Moreover, being relatively young and specialised hampers biotechnology firms' ability to develop commercially-successful drugs. An interpretation of these findings is that biotechnology firms have a superior innovative capacity and inferior commercial capabilities compared to pharmaceutical companies. I will argue that biotechnology firms develop more innovative and medically-important medicines due to extrinsic rather than intrinsic comparative advantages. Additionally, I will argue that biotechnology firms indeed have inferior commercial capabilities compared to pharmaceutical companies.

The relatively good innovative performance of biotechnology firms should not be mistaken for intrinsic innovative superiority. Admittedly, credible arguments exist as to why biotechnology firms can be more intrinsically innovative than pharmaceutical firms. For instance, when developing and commercialising a radically new drug or technology, its potential can better be utilised in an environment without limitations of pre-established routines and specialised assets. Moreover, scientists in biotechnology companies typically enjoy a high degree of autonomy, which is beneficial to creativity and innovation. However, intrinsic advantages of biotechnology firms conducive to innovation are at least to some extent counteracted by limitations in their ability to integrate different knowledge sets (Malerba & Orsenigo, 2015). Integrating different knowledge sets is important and difficult in the drug industry because knowledge is highly fragmented, dispersed and tacit. Biotechnology firms are at a significant disadvantage concerning knowledge integration because of their relatively limited knowledge breadth. Hence, the intrinsic innovative capacity of biotechnology firms should not be exaggerated.

Extrinsic rather than intrinsic factors can better explain the significant development of innovative and medically-important drugs by biotechnology firms. Examples of extrinsic factors include the close relationship of biotechnology firms with academia, biotechnology companies' function of filling in the translational research gap and the financial attractiveness for university scientists to establish a new firm (Pisano, 2006b). Therefore, I recommend biotechnology firms to continue to nurture their bonds with academia and perform translational research. The attribution of biotechnology firms' innovative edge to extrinsic rather than intrinsic factors is significant because it implies that pharmaceutical firms can also reap benefits from these extrinsic factors. Therefore, it is recommended for pharmaceutical firms to invest in the establishment of close partnerships with academia and translational research. In addition, established pharmaceutical firms should design financial reward systems to turn them into more attractive buyers and licensees for university inventions.

Additionally, I argue that biotechnology firms indeed have intrinsically inferior commercial capabilities. At least three valid arguments exist as to why biotechnology firms can have intrinsically inferior commercial capabilities compared to pharmaceutical firms. First, biotechnology firms can have intrinsically inferior commercial capabilities because they have less

commercial experience in a smaller variety of therapeutic areas than pharmaceutical firms. A lower amount of commercial experience comes from being relatively new, specialised and research-focused. Second, biotechnology firms can have worse commercial performance because they are generally smaller in size than pharmaceutical firms and therefore have a smaller salesforce. A small salesforce makes competing with a generally large salesforce of a pharmaceutical firm difficult. Finally, biotechnology companies can have less commercial success than pharmaceutical firms due to path dependencies. The continued dominance of established pharmaceutical firms indicates that path dependencies may be at play.

This study's methodology likely excludes an alternative explanation for the lower sales of biotechnology companies compared to pharmaceutical firms. An alternative explanation is that, instead of being due to poor commercial performance, the lower sales of biotechnology firms is a matter of choice. Biotechnology firms can choose to target less profitable markets because these firms generally have lower growth incentives than pharmaceutical companies. Moreover, less profitable markets can be less competitive. Nevertheless, I adjusted the results of the analyses of commercial success for the targeting of niche markets and the number of potential customers. Therefore, I argue that the relatively poor commercial performance of biotechnology firms compared to pharmaceutical firms is not likely due to the targeting of smaller and less profitable markets. Instead, I argue that the relatively inferior commercial performance of biotechnology firms can be explained by a lack of commercial experience, a smaller salesforce and path dependencies. Hence, I conclude that biotechnology firms indeed have intrinsically inferior commercial capabilities compared to pharmaceutical firms.

Given the relatively inferior commercial performance of biotechnology firms, it is plausible that the development of new biotechnology firms generally has adverse effects on the drug industry's health.[2] The development of new biotechnology firms can harm the industry's health because their poor commercial capabilities limits the number of resources that can be reinvested in R&D. Additionally, the development of new biotechnology firms can impair the drug industry's health because many biotechnology companies fail, which hampers industry-wide learning from failure and knowledge accumulation (Pisano, 2006b).

The notion that the development of biotechnology firms generally has an adverse impact on the pharmaceutical industry's health is significant from a policy perspective. Specific policies vary among countries, but generally, current policies aim at promoting the establishment of new biotechnology firms by stimulating bio-entrepreneurship. A major measure aimed at stimulating bio-entrepreneurship is the promotion of the transfer of intellectual property

[2]It is important to note that this is a generalised statement. Firms and markets in the pharmaceutical industry are in reality not as homogeneous as assumed in the statistical analyses. Therefore, particular situations exist in which the establishment of a new biotechnology firm will likely have a beneficial effect on the drug industry. For instance, the development of a radically new drug or technology can likely better be performed in a new, small, organic and entrepreneurial firm.

from academia to new firms. Due to the superior commercial performance of pharmaceutical firms, policy measures can improve R&D productivity by promoting the transfer of intellectual property to established pharmaceutical firms instead. One way in which the knowledge transfer from academia to established firms can be promoted is by critically reviewing university licensing strategies and policies (Pisano, 2006b). One of the main reasons why university inventions are so often transferred to the industry via new firms instead of existing firms is that a new firm can offer relatively attractive financial rewards. New firms can offer equity in return for intellectual property. In contrast, existing firms can often offer a payment and royalties on sales, which the inventors have to share with the university. Therefore, two examples of policy measures that can be taken are limiting the equity that a university scientist can obtain and increasing the share of the payment and royalties that the university scientists obtain from licensing (Di Gregorio & Shane, 2003).

6.2 New-market disruption by biotechnology firms

The conclusion that biotechnology firms have inferior commercial capabilities compared to pharmaceutical companies may give the impression that the development of the biotechnology sector will not reduce the pharmaceutical R&D productivity decline. However, the conclusion about the future impact of biotechnology firms on R&D productivity is premature when considering that the biotechnology sector is relatively young and its technologies have not matured yet. To gain insights on the future impact of the biotechnology sector on pharmaceutical R&D productivity, I applied disruptive innovation theory, or more specifically, the concept of new-market disruption, to the case of the emerging biotechnology sector. I addressed the second research subquestion: *Are biotechnology firms disrupting the pharmaceuticals market through new-market disruption?* I performed statistical analyses to empirically test the presence of elements of new-market disruption in the drug industry. I assessed whether firms with biotechnological organisational characteristics (the entrants) tend to compete against non-consumption by developing drugs that address previously unmet medical needs for niche markets. In addition, I examined whether firms with pharmaceutical organisational characteristics (the incumbents) tend to target more demanding markets and "over-engineer" their medicinal products.

First, I will discuss the results of the analyses of whether the entrants in the drug industry tend to target unserved customers and niche markets. The results suggest that firms incorporated after 1976, originated from academia and focused on drug discovery and early clinical development are significantly more likely to develop drugs that address unmet medical needs (section 5.2.1). Moreover, the results indicate that firms incorporated after 1976 and originated from universities, research institutes or hospitals are significantly more likely to target niche markets (section 5.2.3). In contrast, the results suggest that being specialised

does not significantly affect a firm's tendency to target unserved customers (section 5.2.1). Additionally, the results indicate that the position in the value chain and the degree of specialisation of the R&D portfolio does not affect a firm's tendency to target niche markets (section 5.2.3). These findings provide some empirical evidence that biotechnology firms tend to target unserved customers and niche markets.

Second, I will discuss the results of the analyses of whether the incumbents in the pharmaceutical industry tend to target more demanding customers and over-engineer their drugs. The results suggest that firms incorporated before 1976 and not originating from academia target significantly larger patient populations (section 5.2.2). In addition, the results indicate that being vertically integrated and having a broad R&D portfolio positively relate to the size of the targeted customer group, although these relationships are not statistically significant. Finally, the results suggest that firms not originating from academia are more likely to develop over-engineered medicines (section 5.2.4). In contrast, the results suggested that no significant effect exists for firms incorporated before 1976, vertically integrated firms and firms with a broad R&D portfolio. These findings provide some empirical evidence that pharmaceutical firms tend to target more demanding markets and over-engineer their medicinal products.

Hence, overall, the findings in this study provide some evidence that biotechnology firms tend to target unserved customers and niche markets, and that pharmaceutical firms tend to target more demanding markets and "over-engineer" their medicines. However, based on these findings, no firm conclusions can be drawn about whether new-market disruption actually *can* and *will* occur in the pharmaceutical industry. To understand whether new-market disruption can and will occur, I will compare one of the very few drug innovations that are believed to be a disruptive innovation, gene therapy (Kapoor & Klueter, 2014), with a classic example of a high-tech disruptive innovation, the disk drive. This comparison will provide arguments that refute the claim that gene therapy is a disruptive innovation and expose why new-market disruption is an improbable event in the pharmaceutical industry.

In the cases of both the disk drives and the gene therapies, the established firms overlooked the disruptive innovation because the performance of that innovation was initially perceived as inferior. In the disk drive industry, established firms did not invest in the development of new smaller disk drives because the storage capacity of smaller disk drives was lower than that of the larger disk drives (Bower & Christensen, 1995). The storage capacity was a performance attribute highly valued by the established firms' main customers: personal computer manufacturers. Therefore, established firms continued to improve the storage capacity of the larger disk drives incrementally - thereby eventually overshooting customer demand - while new firms further developed the smaller disk drives. In the drug industry, established firms shied away from developing gene therapies because of the high safety risks for patients in clinical trials. Complications in clinical trials can seriously damage the reputation of a drug-

developing firm. Therefore, instead of established firms, university and academic spin-outs developed the first gene therapies. Thus, the cases of the disk drive and the gene therapy are similar because established firms initially perceived both innovations as inferior. Moreover, new firms instead of established firms developed both innovations. However, three significant differences between the case of the disk drives and the case of the gene therapies exist.

The first major difference between the two cases relates to differences in the outcome of the competition of consumption against non-consumption in the new market. Because of the inferior storage capacity of the smaller disk drives, the smaller disk drives were initially only valued and used in new markets, such as the portable computer market (Bower & Christensen, 1995). Thus, in the portable computer market, consumption of smaller disk drives won the competition against non-consumption. The case of gene therapies is different. Regulatory agencies do not allow the sales of medical treatments with safety concerns in *any* market, including new markets. Hence, in the case of the inferior gene therapies, non-consumption won the competition against consumption.

The second major difference between the two cases relates to the performance trajectories of disk drives and gene therapies. While being sold in the emerging portable computer market, the storage capacity of the smaller disk drives followed a steep trajectory (Bower & Christensen, 1995). Soon, the storage capacity met the demand of the personal computer manufacturers. Hence, disk drives followed a performance trajectory from a new market to the mainstream market. In contrast to the case of the disk drives, the first gene therapy that a regulatory agency ever approved had a substantial number of potential customers. The first approved gene therapy, developed by a Chinese biotechnology firm, treats head and neck squamous cell carcinoma, which accounts for 10% of the total cancer incidence in China (Pearson et al., 2004). Furthermore, while the nature of gene therapies makes this type of drug very suitable for targeting new small markets by treating rare inherited diseases, biotechnology entrants did not develop gene therapies to cure rare genetic disorders per se. Instead, biotechnology firms developed many gene therapies to treat widespread diseases such as AIDS, heart diseases and cancer (Wirth & Ylä-Herttuala, 2013). Hence, in contrast to disk drives, it can be said that gene therapies followed a performance trajectory from outside the market directly to the mainstream market.

The cases of disk drives and gene therapies differ in a third respect, which concerns the effect of the innovation on the industry. When the smaller disk drives entered the mainstream market, the attributes of the smaller disk drives aligned better with what the mainstream customer valued than those of the larger disk drives (Bower & Christensen, 1995). The smaller disk drives had a “good enough” performance and were sold at a more affordable price, making disk drives and personal computers more accessible. As a result, the smaller disk drives replaced the larger disk drives in the personal computer market and became the

dominant design. When the established firm began to offer smaller disk drives, it was already too late. The new firm with the smaller disk drives already gained market dominance and displaced the established firm. In contrast to disk drives, the emergence of gene therapies has not driven existing medicines or incumbents off the market. Conversely, established firms are major investors in the development of new gene therapies nowadays.

Case-specific arguments can explain the difference between the effect of disk drives and gene therapies on their respective industries. A case-specific explanation is that, while the smaller disk drives were "good enough", more accessible and more affordable, gene therapies are not. Instead, once approved, gene therapies are superior and not more affordable or accessible than existing drugs. Approved gene therapies are superior to existing drugs because they generally offer a one-time cure. Furthermore, gene therapy is currently not more affordable or accessible than existing drugs. Health insurance companies are reluctant to incorporate gene therapies into the standard of care due to the extremely high costs per treatment (over $1 million per treatment) (Barker, 2019).

However, more interestingly, industry-specific aspects can explain the presence of a disruptive effect in the case of disk drives and its absence in the case of gene therapies. Notably in the disk drive industry, the disruptive effect of new firms is common (Bower & Christensen, 1995). Since 1976, no firm has led the industry for more than several years, and no firm that existed before 1976 still exists today. In sharp contrast, in the drug industry, the current leading firms are predominantly established pharmaceutical firms that have dominated the industry for more than a century (Pisano, 2006b). Almost no biotechnology firm has even ever become profitable. I will point out two significant industry-specific reasons why a disruptive effect is common in the disk drive industry and not in the drug industry. I will argue that, in contrast to the disk drive industry, incumbents in the drug industry generally have (1) the sustained revenues and (2) time to respond to technological change, diminishing the disruptive effect caused by new firms.

First, I will illustrate that incumbents in the drug industry can maintain a relatively high level of revenues in response to technological change. Moreover, I will argue that the causes behind the sustained revenues relate to aspects that are specific to the drug industry. These industry-specific aspects include a large number of markets incumbents are active in, the general inability of products in different markets to compete and the generally moderate extent to which innovations are competence-destroying. A comparison of the following two situations will elucidate that the reduced disruptive effect on the pharmaceutical incumbents' revenues arises from a combination of a large number of markets the incumbent firm is active in and the inability of products to diffuse to other markets.

Consider the situation in which a new firm in the disk drive industry successfully develops and markets a smaller disk drive for portable computers. Subsequently, the smaller disk

drive diffuses from the portable computer market to the personal computer market. In the personal computer market, the entrance of the smaller disk drives causes the displacement of the incumbent firm. Since the incumbent firm is mainly active in the personal computer market, the incumbent loses almost all of its revenues to the new firm. Now consider a situation in which a new firm in the drug industry successfully develops and markets a drug to treat, for instance, osteoporosis and manages to displace an incumbent firm in the osteoporosis drug market. The new osteoporosis drug cannot diffuse to another drug market because, except for rare random cases, the same drug cannot treat a different disease. The pharmaceutical incumbent typically sells medicinal products in several markets, and therefore, maintains a substantial revenue stream from drug sales in undisturbed markets. The continued revenue streams provide the incumbent with considerable financial resources to sustain its operations. Hence, pharmaceutical incumbents can maintain a relatively high level of revenues in response to technological change due to their presence in a large number of markets and the inability of products to diffuse to other markets.

Additionally, the reduced disruptive effect that allows incumbents in the drug industry to maintain a considerable level of revenues relates to the extent to which pharmaceutical innovations are competence-destroying. While the emergence of a new disk drive architecture is competence-destroying, breakthrough medicines such as gene therapies do not represent a competence-destroying technological discontinuity per se. Generally speaking, assets such as knowledge, skills, specialised resources and intellectual property do not necessarily become obsolete due to the emergence of a new drug innovation. For instance, medicines can be used in combination. As an example, to slow down the growth of particular tumours, gene therapy can be used to alter the expression of cancer-associated genes in combination with radiation and chemotherapy (Kim et al., 2012). Moreover, medicines are not one-size-fits-all: A variety of medicines is required to treat a variety of people. A treatment effective in one patient may not be effective in another patient. Hence, pharmaceutical incumbents can maintain a relatively high level of revenues in response to technological change because drug innovations are generally moderately competence-destroying.

Second, I will argue that incumbents in the drug industry have relatively more time to respond to technological change. The causes behind the relatively high amount of time relate to aspects that are specific to the drug industry. These industry-specific aspects include a lack of network externalities, the integrality of medicines' product architecture, and the interdependency among drug-developing firms. In the disk drive industry, factors that favour the convergence to a single disk drive architecture in the market are at play (Christensen et al., 1998). Network externalities increase the value of a disk drive in return to adoption. In addition, the modular product architecture of a disk drive allows for component innovation and standardisation. Moreover, a modular product architecture alleviates the need to collaborate with other firms because parts of the product can be developed independently. These factors

contribute to the creation of competition in the disk drive industry that leads to standard battles where there is one winner. When the winner is chosen, it is too late for the incumbent to catch up.

In this respect, the drug industry is very different from the disk drive industry. In contrast to the disk drive industry, no network externalities exist that increase the value of a drug in return to adoption. Furthermore, medicines generally have a highly integral product architecture, which severely hampers component innovation and standardisation. Finally, in contrast to the disk drive industry, drug-developing firms are highly interdependent. The interdependency stems from the integral product architecture of drugs and the fragmented, dispersed and tacit knowledge landscape. Due to the integral product architecture, different components of a drug and their features have to be designed, developed and tested simultaneously.[3] Because knowledge is fragmented, dispersed and tacit, it is nearly impossible to have all capabilities in-house. Therefore, drug-developing firms need each other for complementary capabilities and integral new drug development. As a result of the lack of network externalities, the integrality of medicines' product architecture and the interdependency among drug-developing firms, competition in the drug industry does not result in a moment when a winner is elected.

The industry-specific aspects that explained the diminished disruptive effect in the case of gene therapies are representative of new drug development in general. The industry-specific aspects that diminish the disruptive effect in the drug industry are significant in at least two major respects. First, it explains why, in contrast to the disk drive industry, in the drug industry, arguably no valid previous instances of disruptive innovations can be distinguished and why the new biotechnology firms have not displaced the incumbent pharmaceutical firms. Second, given that the respective industry-specific characteristics of the drug industry are not likely or even impossible to change, it tells us that new-market disruption and displacement of pharmaceutical firms by biotechnology firms are improbable to happen in the future. Therefore, new-market disruption of the pharmaceutical industry by biotechnology firms is not likely to reduce the R&D productivity decline.

From a scientific and strategic management perspective, the notion that industry-specific factors are at play in the drug industry that make the occurrence of disruptive innovation an improbable event - now and in the future - is significant. From a scientific perspective, this conception exposes a deficit in the generalisability of disruptive innovation theory to

[3]New drugs generally consist of two components: the active ingredient and the formulation. The components of a new drug share functions, such as solubility, targeted drug delivery and side-effect minimisation. Functions are interrelated in a very complex manner. For instance, a change in the formulation of a new drug can decrease the side-effects, but can come at the cost of the effectiveness. Due to the decreased effectiveness, a larger dose of the active ingredient may be required, which can, in turn, increase side-effects. Therefore, components of a new drug cannot be designed, developed and tested individually, in contrast to microelectronics such as disk drives.

industries other than the disk drive industry. This study revealed that to apply disruptive innovation theory in a relevant manner, it is important that new products in the industry can be inferior and thereby can follow a performance trajectory, which is not the case in the drug industry. Regulatory agencies only approve a new drug when it is safe and represents an improvement compared to existing drugs. Moreover, this thesis showed that for applying disruptive innovation theory to an industry in a meaningful way, it is important that new firms can have a significant disruptive effect on the incumbents, which is not the case in the drug industry. Industry-specific aspects of the drug industry significantly reduce the disruptive effect new firms can have.

From a strategic management perspective, the idea that the mechanism of new-market disruption does not play a prominent role in the drug industry implies that lessons from new-market disruption should not be taken too seriously. Established pharmaceutical firms can fail because of multiple reasons. Reasons for why these firms fail include high failure rates, long durations and scientific challenges of clinical trials and high regulatory hurdles. Established pharmaceutical firms generally do not fail because they serve their current customers too well. In contrast, pharmaceutical incumbents in the drug industry are continuously looking for biotechnological innovations that can benefit their businesses. Moreover, many incumbents have been able to adopt biotechnological innovations in a timely fashion. Nevertheless, consistent with one of the key lessons of disruptive innovation theory, established pharmaceutical firms should be highly responsive to the technological change and business opportunities that new biotechnology firms bring about.

Instead of deriving strategies from the competitive perspective of the disruptive innovation theory, I urge drug-developing firms to derive strategies from a co-opetitive perspective. Strategies derived from disruptive innovation theory are overly competitive in the context of the drug industry. Biotechnology firms should not aim to disrupt a market and displace pharmaceutical firms. Similarly, the aim of a pharmaceutical firm should not be to prevent biotechnology firms from gaining market share. Strategies derived from disruptive innovation theory fall short of significant mutual opportunities that arise from inter-firm collaboration. Instead of a competitive perspective, inter-organisational dynamics in the pharmaceutical industry are better viewed from a collaborative and competitive perspective. The proposition for drug-developing firms to derive organisational strategies from a co-opetitive perspective is supported by findings from a previous study by Quintana-García and Benavides-Velasco (2004). Quintana-García and Benavides-Velasco (2004) showed that co-opetitive modes of strategic behaviour in the pharmaceutical industry benefit innovation more than collaborative and competitive modes.

The main research question posed in this thesis was: *To what extent can disruption of the pharmaceutical industry by biotechnology firms reduce its R&D productivity decline?* I con-

clude that the development of new biotechnology firms, in their current state, has adverse rather than beneficial effects on R&D productivity. Furthermore, I conclude that disruptive innovation in the drug industry is an improbable process - now and in the future. Moreover, disruptive innovation in the pharmaceutical industry will not have the disruptive effect to provide the drastic reform the industry needs to improve its R&D productivity. Therefore, disruption of the pharmaceutical industry by biotechnology firms will not reduce the pharmaceutical R&D productivity decline.

Chapter 7

Conclusion and reflection

7.1 Conclusion

This thesis aimed to analyse to what extent disruption by biotechnology firms can contribute to reducing the pharmaceutical R&D productivity decline. Based on analyses of biotechnology firms in relation to R&D productivity and new-market disruption, I concluded that disruption by biotechnology firms does not reduce the pharmaceutical R&D productivity decline. The development of new biotechnology firms likely has adverse rather than beneficial effects on R&D productivity. Moreover, new-market disruption in the drug industry is an improbable process that will not provide the drastic reform the industry needs to improve its R&D productivity.

Based on the results from quantitative analyses of the relationships of biotechnological organisational characteristics and determinants of R&D productivity, it was concluded that biotechnology firms make use of extrinsic rather than intrinsic comparative innovative advantages. The results suggest that new firms and academic spin-outs have better odds at developing innovative and medically-important drugs. However, this finding was attributed to extrinsic rather than intrinsic factors. Examples of extrinsic factors are the close relationship with academia, the function of filling in the translational research gap and the financial attractiveness for university scientists to establish a new firm. Therefore, it is recommended for biotechnology firms to nurture their bonds with academia. Moreover, I urge pharmaceutical firms to invest in establishing close partnerships with academia and translational research and improving financial rewards for university scientists in return for their intellectual property.

Furthermore, it was concluded that biotechnology firms have intrinsically inferior commercial capabilities compared to pharmaceutical firms. The results indicate that academic spin-outs and firms focused on drug discovery and early development do not have better odds of commercial success. New firms and specialised firms are even significantly less likely to develop

commercially-successful medicines. The lower probability of developing commercially successful drugs for biotechnology firms can be attributed to intrinsically inferior commercial capabilities compared to pharmaceutical companies. Biotechnology firms have relatively less commercial experience, a smaller salesforce and are at a disadvantage of path dependencies. It is beneficial for the financial health of the drug industry to promote the intellectual property transfer from academia to established firms instead of new firms. Intellectual property transfer from academia to established pharmaceutical firms can be stimulated by reviewing university licensing strategies and policies. Recommended policy revisions include the limitation of equity and the increase of the royalties share university scientists can obtain for their intellectual property.

Additionally, it was concluded that the biotechnological organisational characteristic of being specialised corresponds to a significantly lower R&D productivity performance considering all three investigated determinants. Based on this finding, it is recommended for drug-developing firms to invest in a broad rather than a specialised R&D portfolio. The investment in a broad R&D portfolio allows a drug-developing firm to enjoy economies of scope, better integrate different sets of knowledge, and better recognise a drug candidate's commercial potential. Interestingly, the proposition of investing in a broad R&D portfolio contradicts the strategic advice to specialise in specific therapeutic areas to gain a comparative advantage. While the investment in a broad R&D portfolio is feasible for established pharmaceutical firms, it is not straightforward for resource-constrained biotechnology firms. For specialised biotechnology firms, it is recommended to gain access to a diverse pool of shared knowledge via the establishment of intimate long-term relationships with other drug-developing firms. Harnessing venture philanthropy is an excellent way for biotechnology firms to gain access to a network of diverse knowledge, long-term strategic partnerships and capital investments.

The findings that biotechnology firms have better odds at developing innovative and medically-important medicines due to extrinsic factors and have worse commercial capabilities have significant implications. Most importantly, they imply that the development of new biotechnology firms - in their current state - likely is adverse rather than beneficial for R&D productivity. Nevertheless, the biotechnology sector is still relatively immature and therefore, the future can be different. Therefore, I examined the future effect of biotechnology firms on the pharmaceutical industry using disruptive innovation theory as a framework.

Results of the quantitative analyses of the relationships between biotechnology firms and elements of new-market disruption can be interpreted as empirical evidence that biotechnology firms are disrupting the pharmaceutical industry. The results suggest that biotechnology firms tend to develop drugs that address previously unmet medical needs in niche markets. Moreover, they suggest that pharmaceutical firms target larger patient populations and over-engineer their medicines. Nevertheless, I refuted the interpretation of these results as empirical

evidence that biotechnology firms are disrupting the pharmaceuticals market. Instead, I concluded that the results indicate that biotechnology firms target less competitive markets than pharmaceutical firms due to biotechnology firms' relatively weak commercial capabilities.

The hypothesis that biotechnology firms are disrupting the pharmaceutical industry was rejected due to two major limitations encountered during the application of disruptive innovation theory to the pharmaceutical industry. A first limitation is that disruptive innovation theory can only be applied to drugs that are initially inferior in terms of other performance attributes than safety, such as the frequency or invasiveness of the treatment. Considering that drug innovations are commonly associated with safety risks, this limitation represents a significant decrease in the extent to which strategic management lessons of disruptive innovation theory can be practically applied. A second limitation concerns industry-specific aspects of the drug industry that make new-market disruption and displacement of pharmaceutical firms by biotechnology firms an improbable process that cannot provide the drastic reform the pharmaceutical industry needs to improve its R&D productivity. Pharmaceutical incumbents have a comparatively high level of sustained revenues and time to respond to the technological change that new biotechnology firms bring about. Combined with the results of the current impact of biotechnology firms on R&D productivity, this finding leads to the conclusion that new-market disruption of the pharmaceutical industry by biotechnology firms does not and will not reduce its R&D productivity decline.

The conclusion that new-market disruption of the pharmaceutical industry by biotechnology firms does not improve R&D productivity implies that drug-developing firms should focus on alternative organisational strategies. I recommend drug-developing firms to adopt organisational strategies that are more appropriate considering the inter-organisational dynamics in the drug industry. I argue that strategies derived from a co-opetitive instead of a competitive perspective in the context of the pharmaceutical industry will be more beneficial for R&D productivity on the firm and the industry level.

The findings in this thesis can potentially be generalised to industries that are also characterised as science-based industries, such as the nanotechnology industry. Science-based businesses have in common that new product development requires long high-risk investments due to technological uncertainty and that firms are likely to be interdependent (Pisano, 2006b, 2010). New product development requires long high-risk investments because the science is still immature and therefore, product development is often a trial-and-error process aimed at generating new scientific knowledge rather than applying scientific knowledge. Science-based businesses are likely to be interdependent due to integral product architectures. Product architectures in science-based industries are likely to be integral because science is the product and when science is immature, scientific problems can often not simply be split into smaller problems. Science-based industries are significantly different from other high-tech industries.

In high-tech industries, such as the microelectronics industry, product development is generally based on an existing and mature body of science. As a result, new product development is much less risky, requires shorter investment horizons and can be split into modular tasks. Thus, while most findings of this thesis do not seem to be generalisable to other high-tech industries, the shared features of the drug industry and other science-based industries can allow the findings to be valuable to promoting innovation and performance in science-based businesses in general.

7.2 Reflection

7.2.1 Practical relevance

From a managerial perspective, this thesis is significant because it identified fundamental reasons why executives of drug-developing firms should be hesitant to adopt organisational strategies developed based on general high-tech industries, such as the disk drive industry. The drug industry is significantly different from traditional high-tech industries. Therefore, the mechanisms underlying successful strategies in other high-tech industries may not apply to the drug industry. This thesis demonstrated how atypical the drug industry is compared to a traditional high-tech industry. Moreover, this thesis showed how strategies from one of today's most influential business theories, disruptive innovation theory, can only be applied to the drug industry to a very limited extent. Besides strategies developed based on traditional high-tech industries, executives of firms in the pharmaceutical industry should be cautious of adopting organisational strategies that stimulate highly competitive behaviour. Drug-developing firms are highly interdependent. As a result, drug-developing firms benefit more from organisational strategies that, depending on the situation, pursue zero-sum or positive-sum gains.

From a policy perspective, this thesis contributes to the debate on whether current policies aimed at stimulating pharmaceutical R&D productivity are effective. Findings in this thesis are significant from a policy perspective because the findings support the somewhat controversial proposition that the stimulation of the development of new biotechnology firms is not beneficial for R&D productivity. In contrast to previous studies arguing against stimulating the development of new biotechnology firms, a major strength of this thesis is that empirical data support the arguments. Nevertheless, it should be noted that previous public investments are not all for nothing. Public investments in interdisciplinary education and basic research for drug innovation and public spending and policies promoting bio-entrepreneurship continue to benefit R&D productivity. However, the promotion of bio-entrepreneurship only improves R&D productivity when the innovation benefits of establishing a new firm outweigh the costs of knowledge integration and commercialisation. Due to the COVID-19 pandemic, more public money is being channelled to the pharmaceutical industry than ever before. The present study's policy revision propositions contribute to ensuring that current financial stimuli reach

their potential for improving pharmaceutical R&D productivity in the long term.

Finally, from a societal perspective, findings in this thesis relate to a significant societal issue in a large part of the world: the affordability and accessibility of medicines. Multiple recommendations in this thesis can make a valuable contribution to making future medical treatments more affordable and accessible. Established pharmaceutical firms, often referred to as "big pharma", are frequently criticised for disproportionate drug pricing that jeopardises the affordability and accessibility of healthcare. It is true that some pharmaceutical firms demand disproportionally high prices for medicines in pursuit of commercial interests. However, in my view, the relatively high drug pricing is for most of the big pharma a mere symptom of the R&D productivity decline and the incredibly high scientific and technological uncertainty in drug R&D. Pharmaceutical firms have an increasing inability to reap returns from R&D investments. Therefore, solely demanding lower prices for medicines will not improve the long-term affordability and accessibility of healthcare. Conversely, it will have detrimental effects on future drug innovation. This thesis is relevant from a societal perspective because it proposes alternative solutions to the artificial lowering of drug prices which harbour the potential to provide long-term advantages.

7.2.2 Scientific relevance

This thesis offers relevant contributions to scientific research on patterns of innovation and management practices in the pharmaceutical industry. This study addresses the interesting observation that while biotechnology advocates expected the emergence of a Schumpeter Mark I pattern of innovation (Schumpeter, 1911), an innovation pattern according to Mark II persists (Schumpeter, 1942). This study's findings support the view that established firms are more likely to succeed in response to industry-wide technological changes than new firms (Schumpeter, 1942; Tushman & Anderson, 1986; Henderson & Clark, 1990; Christensen & Bower, 1996). The persistence of a creative accumulation pattern of innovation rather than the emergence of a creative destruction pattern is arguably explainable considering the dimensions of the pharmaceutical industry's technological regime (Breschi et al., 2000). The industry's technological regime is characterised by low technological opportunity and a knowledge base close to basic science, which work towards creative accumulation.

Additionally, the present study offers new insights into prominent issues in scientific research on management practices in the pharmaceutical industry. Examples of important issues addressed in this study are whether a drug-developing firm should vertically integrate or disintegrate and whether knowledge depth or breadth is conducive to drug innovation. Remarkably, this thesis is the first empirical study to suggest that no comparative advantage exists for vertical integration or disintegration at the industry level. In addition, this study validates findings from previous studies that showed that economies of scope in drug research exist

(Henderson & Cockburn, 1996). Interestingly, findings from the present study complement previous studies by suggesting that economies of scope exist in both drug research and commercialisation.

7.2.3 Limitations

This study is limited in four ways. The first limitation concerns defining biotechnology and pharmaceutical firms. The methodology used to define a biotechnology and a pharmaceutical firm represents an important step towards adequate definitions. Nevertheless, the results from the reliability analysis suggest that the current reliability of the measurement of a biotechnology and a pharmaceutical firm can still be improved.

A second limitation of the present study concerns the determination of R&D productivity. I did not include some important determinants of R&D productivity, such as costs, attrition rates and duration of clinical trials, due to a lack of publicly available data. Since no data on R&D costs could be gathered, I estimated the commercial performance of firms based on drug sales of new drugs instead of profitability. Because almost no biotechnology firm has ever been profitable to date, the estimation of commercial performance based on profitability likely provides an even more pessimistic image of biotechnology firms' commercial capabilities. Furthermore, the estimation of commercial success based on new drugs neglects sales from previous drugs. Since biotechnology firms generally have fewer sales from previous products than pharmaceutical firms (or even no sales from previous products at all), the consideration of sales from previous drugs also disfavours biotechnology firms.

A third limitation stems from the approach of observing elements of new-market disruption in empirical data. I performed quantitative industry-level analyses to test for the presence of elements of new-market disruption. This approach is in contrast to many previous studies, which used a qualitative case study approach. The use of quantitative analyses limits the depth of the study because it does not allow qualitative elements of new-market disruption to be observed. However, the approach of a quantitative industry-level analysis is beneficial because it enhances the generalisability of the findings. A lack of generalisability is a common critique on applications of disruptive innovation theory to case studies.

A fourth limitation of this thesis corresponds to the sample and type of the data. Due to a lack of publicly available data on failed R&D projects, the data sample only contained new drug applications that the FDA successfully approved. As a result, this study's findings can be biased due to location and survival effects. While the location bias is minimal, survival effects can bias this study's results in unexpected ways. Furthermore, data on whether a drug was innovative, medically important, targeted a niche market or a new market are indirect measures based on secondary data from the FDA. Therefore, the data can be biased due to errors and human decision-making. Nevertheless, no good alternatives to using these indirect

measured currently exist.

7.2.4 Recommendations for future research

Future studies should be performed using additional data on failed R&D projects and R&D costs to corroborate the present study's findings and the proposed measures to stimulate R&D productivity. Furthermore, while this study assumed the drug industry to be as homogeneous among markets, future studies should reveal to what extent the industry-level findings can be applied to specific drug markets. Moreover, future studies into the effect of independent research units in established firms on R&D productivity can provide interesting and valuable additions or nuances to current findings. Finally, future management science studies should focus on researching organisational strategies for drug-developing firms from a co-opetitive perspective. An example of a relevant future study is to consider inter-firm relationships in the pharmaceutical industry through a game-theoretic framework.

7.2.5 Management of Technology perspective

This master thesis is my final product for the Master of Science in Management of Technology programme. This thesis had to fulfil three requirements. It needed to *"report on a scientific study in a technological context, show an understanding of technology as a corporate resource ... [and be] based on scientific methods and techniques to analyse a problem as put forward in the curriculum"* (TU Delft, 2021). In this thesis, I analysed the problem under investigation using hypothesis testing and quantitative research methods as put forward in "Social and Scientific Values" and "Research Methods". Furthermore, the course "Leadership and Technology Management" provided me with a relevant understanding of how knowledge management influences innovation. Important concepts introduced were, among others, organisational learning, absorptive capacity, open innovation models and difficulties associated with complex projects such as new drug development. By following the course "Technology, Strategy and Entrepreneurship", I obtained valuable knowledge of aspects of organisational strategies, new product development and entrepreneurship. These aspects included, among others, causes of incumbent inertia, advantages of small versus large corporations, reasons for collaboration, advantages of innovation protection versus diffusion, disruptive innovation and patterns of innovation. I analysed the problem, the decreasing pharmaceutical R&D productivity, in the context of fast biotechnological progress. Throughout this thesis, accelerating and improving drug innovation and reaping the full potential of biotechnological advancements as a means to restore the economic health of drug-developing firms was the central theme.

7.2.6 Author's reflection

When I started the Master Thesis Project, my thesis was planned to become different from what it is. I learned that it is very important to anticipate possible setbacks in research and to have a solid plan B. In retrospect, if I could redo this thesis project, I would have limited the amount of primary data that I collected. The collection of primary data was time-consuming. Some time spent on primary data collection could have been devoted to, for instance, diving deeper into the defining features of biotechnology and pharmaceutical firms. As an example, some results suggest that *Specialisation* may not be such a defining feature after all. *Specialisation* was negatively correlated with productivity determinants and elements of new-market disruption where other organisational characteristics were positively correlated. Furthermore, time could have been devoted to interviewing executives of drug-developing firms to corroborate this study's results and their interpretations. Nevertheless, a clear benefit of the larger amount of data is that it enhanced the statistical power of the tests.

During the Master Thesis Project, I encountered, solved and learned from multiple issues. I came across a first difficulty early on in the process: the large scope and complexity of the pharmaceutical R&D productivity decline. After much reading and writing about the subject, I successfully found a scientifically and practically relevant knowledge gap that was very close to my interests. The impact of biotechnology firms on pharmaceutical R&D productivity was revealed to be an important topic from a societal, organisational and policy perspective but is poorly understood.

The second difficulty became a major issue: obtaining data to perform quantitative analyses. Much time and effort were spent on contacting research institutes, scholars and business intelligence companies. However, data on drug development used in previous studies are proprietary and very expensive. Luckily, in December, I contacted a professor who agreed to provide me with proprietary data under the constraint that I sign a non-disclosure agreement. Based on the agreement that I would obtain the required data for my analyses, I drafted a master thesis proposal and started my master thesis project. Unfortunately, in March, I obtained the news that I could no longer use the proprietary data. While there was a plan B that I could fall back on, I was obliged to alter a significant part of my proposed study. Instead of obtaining data on more than 20.000 R&D projects that failed and succeeded in the past 40 years, I gathered data on 837 successful new drug applications between 2008 and 2015. Implications for my research were that my data were biased to R&D projects that were successful and approved in the US and that I could not include other R&D determinants in my analysis, such as attrition rates, durations of clinical trials and costs. Moreover, it restricted me from analysing the applicability of findings to therapeutic areas and types of medicines. Additionally, much time had to be spent on data collection, which came at the cost of exploring interesting outcomes more in-depth, for instance, via interviews. As an upside,

the drastic decrease in data allowed me to assess each of the companies responsible for the new drug based on multiple organisational characteristics. The assessment of drug-developing firms based on multiple organisational characteristics proved to be valuable for interpreting the results from data analyses.

A final issue that I encountered was my initial lack of knowledge and experience in performing statistical research. Much time and effort were invested in gaining knowledge and experience in performing statistical tests, getting acquainted with SPSS and exploring and analysing data. I learned that I enjoy analysing large sets of data. Therefore, this difficulty turned into a valuable and interesting learning experience.

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Appendix A

Reliability analyses of organisational characteristics

A.1 Inter-item correlations

Table A.1: Inter-item non-parametric Spearman correlations of organisational characteristics of companies in sample 1 involved in phase I.

	Age	*Location*	*Origin*	*Position Value Chain*	*Specialisation*	*Riskiness R&D Projects*	*Collaboration*
Age	1.000						
Location	-0.058 (0.322)	1.000					
Origin	0.230** (0.000)	-0.110 (0.060)	1.000				
Position Value Chain	0.455** (0.000)	-0.175** (0.003)	0.220** (0.000)	1.000			
Specialisation	0.397** (0.000)	-0.228** (0.000)	0.147** (0.011)	0.252** (0.000)	1.000		
Riskiness R&D Projects	-0.125* (0.032)	0.327** (0.000)	0.011 (0.845)	-0.131* (0.024)	-0.368** (0.000)	1.000	
Collaboration	-0.266** (0.000)	0.054 (0.352)	0.136* (0.020)	-0.208** (0.000)	-0.075 (0.198)	0.152** (0.004)	1.000

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

Table A.2: Inter-item non-parametric Spearman correlations of organisational characteristics of companies in sample 1 involved in phase II.

	Age	*Location*	*Origin*	*Position Value Chain*	*Specialisation*	*Riskiness R&D Projects*	*Collaboration*
Age	1.000						
Location	-0.041 (0.478)	1.000					
Origin	0.204** (0.000)	-0.128* (0.027)	1.000				
Position Value Chain	0.396** (0.000)	-0.188** (0.001)	0.239** (0.000)	1.000			
Specialisation	0.086** (0.000)	-0.252** (0.000)	0.149** (0.010)	0.191** (0.001)	1.000		
Riskiness R&D Projects	-0.100 (0.084)	0.339** (0.000)	0.004 (0.947)	-0.130 (0.077)	-0.370** (0.000)	1.000	
Collaboration	-0.278** (0.000)	0.108 (0.062)	0.118* (0.042)	0.173** (0.003)	-0.103 (0.077)	0.159** (0.006)	1.000

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

Table A.3: Inter-item non-parametric Spearman correlations of organisational characteristics of companies in sample 1 involved in phase III.

	Age	*Location*	*Origin*	*Position Value Chain*	*Specialisation*	*Riskiness R&D Projects*	*Collaboration*
Age	1.000						
Location	-0.105 (0.074)	1.000					
Origin	0.183** (0.002)	-0.116* (0.047)	1.000				
Position Value Chain	0.340** (0.000)	-0.162** (0.005)	0.280** (0.000)	1.000			
Specialisation	0.431** (0.000)	-0.237** (0.000)	0.130** (0.026)	0.152** (0.009)	1.000		
Riskiness R&D Projects	-0.183* (0.002)	0.338** (0.000)	0.051 (0.387)	-0.064 (0.278)	-0.354** (0.000)	1.000	
Collaboration	-0.268** (0.000)	0.118 (0.043)	0.135* (0.021)	-0.094 (0.107)	0.063 (0.282)	0.158** (0.007)	1.000

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

Table A.4: Inter-item non-parametric Spearman correlations of organisational characteristics of companies in sample 1 involved in FDA application.

	Age	*Location*	*Origin*	*Position Value Chain*	*Specialisation*	*Riskiness R&D Projects*	*Collaboration*
Age	1.000						
Location	-0.088 (0.127)	1.000					
Origin	0.252** (0.000)	-0.019 (0.749)	1.000				
Position Value Chain	0.331** (0.000)	-0.108 (0.063)	0.227** (0.000)	1.000			
Specialisation	0.401** (0.000)	-0.182** (0.000)	0.116** (0.045)	0.163** (0.005)	1.000		
Riskiness R&D Projects	-0.114* (0.049)	0.363** (0.000)	0.084 (0.147)	-0.040 (0.495)	-0.267** (0.000)	1.000	
Collaboration	-0.241** (0.000)	0.165** (0.004)	0.135* (0.019)	-0.079 (0.175)	-0.051 (0.382)	0.175** (0.002)	1.000

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

Table A.5: Inter-item non-parametric Spearman correlations of organisational characteristics of companies in sample 1 involved in marketing.

	Age	*Location*	*Origin*	*Position Value Chain*	*Specialisation*	*Riskiness R&D Projects*	*Collaboration*
Age	1.000						
Location	-0.131* (0.023)	1.000					
Origin	0.248** (0.000)	-0.184** (0.001)	1.000				
Position Value Chain	0.367** (0.000)	-0.110 (0.056)	0.376** (0.000)	1.000			
Specialisation	0.417** (0.000)	-0.215** (0.000)	0.238** (0.000)	0.204** (0.000)	1.000		
Riskiness R&D Projects	-0.150** (0.009)	0.265** (0.000)	-0.062 (0.281)	-0.052 (0.368)	-0.278** (0.000)	1.000	
Collaboration	-0.272** (0.000)	0.065 (0.262)	0.112* (0.034)	0.016 (0.779)	-0.049 (0.421)	0.156** (0.007)	1.000

* Correlation is significant at the $p \leq 0.05$ level (two-tailed)

** Correlation is significant at the $p \leq 0.01$ level (two-tailed)

A.2 Internal consistency analysis

Table A.6: Results of internal consistency analysis of organisational characteristics used to define biotechnology and pharmaceutical firms.

Subject of analysis	Cronbach's alpha				
	Phase I	Phase II	Phase III	FDA Applicant	Marketer
All seven organisational characteristics	0.211	0.188	0.197	0.328	0.250
organisational characteristics excluding location, riskiness and collaboration	0.621	0.593	0.589	0.579	0.621

Appendix B

Excluded NDAs from sample 1

Table B.1: Excluded NDAs from sample 1.

US trade name	Drug name	Approval Year	FDA Applicant	Reason for exclusion
Lexiscan	Regadenoson	2008	CV Therapeutics	Not a drug
Eovist	Gaoxetate disodium	2008	Bayer	Not a drug
AdreView	Iobenguane I 123	2008	GE Healthcare	Not a drug
Lusedra	Fospropofol disodium	2008	Eisai Medical Research	Not a drug
Vasovist	Gadofosveset trisodium	2008	Epix Pharmaceuticals	Not a drug
DaTscan	Ioflupane I 123	2011	GE Healthcare	Not a drug
Gadavist	Gadobutrol	2011	Bayer	Not a drug
Amyvid	Florbetapir F 18	2012	Avid Radiopharmaceuticals	Not a drug
Prepopik	Sodium picosulfate, magnesium oxide, citric acid	2012	Ferring Pharmaceuticals	Not a drug
-	Choline C 11	2012	Mayo Clinic	Not a drug
Lymphoseek	Technetium Tc 99m tilmanocept	2013	Navidea Biopharmaceuticals	Not a drug
Dotarem	Gadoterate meglumine	2013	Guerbet	Not a drug
Vizamyl	Flutemetamol F 18	2013	GE Healthcare	Not a drug
Neuraceq	Florbetaben F 18	2014	Piramal Imaging	Not a drug
Lumason	Sulfur hexafluoride lipid-type A microspheres	2014	Bracco Diagnostics	Not a drug

Appendix C

Excluded NDAs from sample 2

Table C.1: Excluded NDAs from sample 2.

US trade name	Drug name	Reason for exclusion	US trade name	Drug name	Reason for exclusion
Accretropin	Somatropin	no submission classification	Raxibacumab	Raxibacumab	no submission classification
Arcalyst	Rilonacept	no submission classification	Oxycodone Hydrochloride	Oxycodone Hydrochloride	drug already marketed
Cimzia	Certolizumab Pergol	no submission classification	Adrenalin	Epinephrine	drug already marketed
Nplate	Romiplostim	no submission classification	Phenylephrine Hydrochloride	Phenylephrine Hydrochloride	drug already marketed
Morphine Sulfate	Morphine Sulfate	drug already marketed	Nitrous Oxide	Nitrous Oxide	not a drug
Mycifradin	Neomycin Sulfate	no submission classification	Oxygen	Oxygen	not a drug
Simponi	Golimumab	no submission classification	Nitrogen	Nitrogen	not a drug
Dysport	Abobotulinum toxin A	no submission classification	Carbon Dioxide	Carbon Dioxide	not a drug
Creon	Pancrelipase	no submission classification	Helium	Helium	not a drug
Ilaris	Canakinumab	no submission classification	Simponi Aria	Golimumab	no submission classification
Extavia	Interferon Beta-1B	no submission classification	Actemra	Tocilizumab	no submission classification
Zenpep	Pancrelipase	no submission classification	Gazyva	Obinutuzumab	no submission classification
Stelara	Ustekinumab	no submission classification	Vimizim	Elosulfase Alfa	no submission classification
Arzerra	Ofatumumab	no submission classification	Myalept	Metreleptin	no submission classification
Kesimpta	Ofatumumab	no submission classification	Nexium 24HR	Esomeprazole Magnesium	Rx-to-OTC switch
Nicardipine Hydrochloride	Nicardipine Hydrochloride	no submission classification	Tanzeum	Albiglutide	no submission classification
Kalbitor	Ecallantide	no submission classification	Sylvant	Siltuximab	no submission classification

Table C.1 – continued from previous page

US trade name	Drug name	Reason for exclusion	US trade name	Drug name	Reason for exclusion
Codeine Sulfate	Codeine Sulfate	drug already marketed	Entyvio	Vedolizumab	no submission classification
Colcrys	Colchicine	drug already marketed	Afrezza	Insulin Recombinant Human	no submission classification
Actemra	Tocilizumab	no submission classification	Flonase Allergy Relief	Fluticasone Propionate	Rx-to-OTC switch
Vpriv	Velaglucerase Alfa	no submission classification	Keytruda	Pembrolizumab	no submission classification
Pancreaze	Pancrelipase	no submission classification	Trulicity	Dulaglutide	no submission classification
Lumizyme	Alglucosidase Alga	no submission classification	Blincyto	Blinatumomab	no submission classification
Prolia	Denosumab	no submission classification	Opdivo	Nivolumab	no submission classification
Xgeva	Denosumab	no submission classification	Vasostrinct	Vasopressin	drug already marketed
Xeomin	Incobotulinum toxin A	no submission classification	Potassium Chloride	Potassium Chloride	drug already marketed
Krystexxa	Pegloticase	no submission classification	Consentyx	Secukinumab	no submission classification
Egrifta	Tesamorelin Acetate	no submission classification	Natpara	Parathyroid Hormone	no submission classification
Oxycodone Hydrochloride	Oxycodone Hydrochloride	drug already marketed	Toujeomax Solostar	Insulin Glargine Recombinant	no submission classification
Children's Allegra Allergy	Fexodenadine Hydrochloride	Rx-to-OTC switch	Medical Air	Medical Air	not a drug
Benlysta	Belimumab	no submission classification	Zarxio	Filgrastim-SNDZ	no submission classification
Yervoy	Ipilmumab	no submission classification	Unituxin	Dinutuximab	no submission classification
Nulojix	Belatacept	no submission classification	Humalog Kwikpen	Insulin Lipro Recombinant	no submission classification
Adcetris	Brentuximab Vedotin	no submission classification	Praluent	Alirocumab	no submission classification
Levothyroxine Sodium	Levothyroxine Sodium	drug already marketed	Tresiba	Insulin Degludec	no submission classification
Morphine Sulfate	Morphine Sulfate	drug already marketed	Praxbind	Idarucizumab	no submission classification
Hydromorphone Hydrochloride	Hydromorphone Hydrochloride	drug already marketed	Strensiq	Asfotase Alfa	no submission classification
Voraxaze	Glucarpidase	no submission classification	Nucala	Mepoloizumab	no submission classification
Viokace	Pacrelipase	no submission classification	Darzalex	Daratimumab	no submission classification
Elelyso	Taliglucerase Alfa	no submission classification	Portrazza	Necitumumab	no submission classification
Perjeta	Pertuzumab	no submission classification	Empliciti	Elotuzumab	no submission classification
Zaltrap	Ziv-Aflibercept	no submission classification	Kanuma	Sebelipase Alfa	no submission classification

Table C.1 – continued from previous page

US trade name	Drug name	Reason for exclusion	US trade name	Drug name	Reason for exclusion
Granix	Tbo-Filgrastim	no submission classification	Basaglar	Insulin Glargine	no submission classification
Oxytrol for women	Oxybutynin	Rx-to-OTC switch	Cyramza	Ramucirumab	no submission classification
Jetrea	Ocriplasmin	no submission classification	Zegerid	Omeprazole; Sodium Bicarbonate	Rx-to-OTC switch
Plegridy	Peginterferon Beta-1A	no submission classification	Repatha	Evolocumab	no submission classification
Desmopressin Acetate	Desmopressin Acetate	no information about designation	Eylea	Aflibercept	no submission classification
Xiaflex	Collagenase Clostridium Histolyticum	no submission classification	Erwinaze	Asparaginase Erwinia Chrysanthemi	no submission classification
Kadcyla	Ado-Trastuzumab Emtansine	no submission classification	Ryzodeg	Insulin Aspart; Insulin Degludec	no submission classification
Novolog 50/50 Mix	Insulin Aspart Protamine Recombinant and Insulin Aspart Recombinant	no submission classification			