Curing a 70-year-old disease

The factors behind the turnaround in pharmaceutical R&D productivity

Bachelor's thesis in Industrial Engineering and Management

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Att bota en 70-årig sjukdom

Faktorerna bakom produktivitetsskiftet inom läkemedelsutveckling

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Abstract

Problem: The pharmaceutical industry has for a long time been characterized by exponentially declining R&D productivity, which even got its own term – Eroom's law. The R&D productivity has in the last ten years experienced a turnaround, and the factors underlying this productivity increase are yet to be fully understood. The underlying factors must be well understood so that the productivity turnaround can be preserved and continue in the future.

Aim: The report aims to investigate the underlying factors to the R&D productivity turnaround.

Method: The study is divided into two parts: one literature study of previous research, and one interview study with Swedish industry experts. It has an abductive approach, basing the findings on the existing theory and complementing it with experience and knowledge from interview respondents.

Results and implications: The result highlights six main factors that relate to the turnaround in R&D productivity. These are the types of drugs developed and the role of increased scientific understanding, externalization of R&D, the role of the regulators, the development of clinical trials, the role of digital technology, and the role of managerial efforts. Implications regarding key differentiation between external and internal factors as well as the longevity of the productivity increase are further discussed.

Conclusion: The study concludes that previous research conforms well to the perspective of the respondents, with particular emphasis on the importance of greater scientific understanding, increased specialization, regulatory incentives and flexibility, and efficient managerial efforts. A conceptual framework is also provided that can be used to better understand the intercorrelation between the different factors.

Keywords: Research and development, R&D, pharmaceutical industry, drug discovery, clinical trials, attrition rates, adaptive clinical trial designs, R&D productivity, Eroom’s law, pharmaceutical innovation.

Note: The report is written in English.

Sammanfattning

Problem: Läkemedelsindustrin har länge karaktäriserats av exponentiellt avtagande FoU-produktivitet, vilket till och med har fått ett eget begrepp – Erooms lag. FoU-produktiviteten har under de senaste tio åren uppvisat en ökning, men faktorerna som ligger bakom denna produktivitetsökning är fortfarande inte helt förstådda. Det är viktigt att de underliggande faktorerna kartläggs grundligt för att skiftet i FoU-produktivitet ska kunna bevaras och fortsätta i framtiden.

Syfte: Målet med rapporten är att undersöka de underliggande faktorerna till skiftet i R&D-produktivitet.

Metod: Studien är uppdelad i två delar: en litteraturstudie som berör tidigare forskning samt en intervjustudie med svenska industriexperter. Den har ett abduktivt tillvägagångssätt, där resultatet baseras på existerande teorier som kompletteras med erfarenhet och kunskap från intervjurespondenterna.

Resultat och implikationer: Resultatet lyfter fram sex huvudsakliga teman som relaterar till skiftet i R&D produktivitet. Dessa är typerna av utvecklade läkemedel och rollen av ökad vetenskaplig förståelse, externalisering av FoU, rollen av regulatoriska myndigheter, utvecklingen av kliniska försök, rollen av digital teknologi, och rollen av styrningsmetoder. Implikationer kopplade till de största skillnaderna mellan externa och interna faktorer samt långvarigheten i produktivitetsökningen diskuteras ytterligare.

Slutsats: Studien kommer fram till att tidigare forskning överensstämmer väl med perspektivet hos respondenterna, med särskild betoning på betydelsen av ökad vetenskaplig förståelse, ökad specialisering, regulatoriska incitament och flexibilitet, och effektiva styrningsmetoder. Ett konceptuellt ramverk som kan användas för att bättre förstå kopplingen mellan de olika faktorerna presenteras också.

Nyckelord: Forskning och utveckling, FoU, läkemedelsindustri, läkemedelsutveckling, kliniska studier, FoU produktivitet, klinisk adaptiv försöksdesigner, Erooms lag, läkemedelsinnovation.

Notera: Rapporten är skriven på engelska.

Preface

This bachelor's thesis was written during the Spring of 2021 at the Department of Technology Management and Economics at Chalmers University of Technology by six students from Industrial Engineering and Management.

Not only has the study been educative for the authors, but it has also led to many interesting discussions with inspiring individuals.

Gratitude is directed towards our supervisor Anders Isaksson and our industry supervisor Francesco Gatto, for their knowledge and great commitment. Also, gratitude is directed to all the interviewees who graciously agreed to share their knowledge, experience, and time.

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Table of content

1. Introduction

Today, it is well established that the biggest obstacle when it comes to innovation management is the uncertainty of outcomes, and in today's ever-changing climate it is harder than ever to plan and navigate the path to innovation success (Granstrand, 2018). For example, the pillar stone of innovation – research and development (R&D) – is characterized by uncertain revenue streams, long time horizons, high policy risk, and often demands very large initial investments (Granstrand, 2018).

With a global average R&D cost of $1.3B to bring a new pharmaceutical drug to market (Wouters et al., 2020), the pharmaceutical industry is one of the biggest R&D-spenders in the world (Statista, 2020). Since only 7.9 % of pharmaceuticals end up successful, the risks, costs, and stakes are all uniquely high (Thomas et al., 2021). However, for the few that succeed, massive profits and return on investment await (Tsai & Erickson, 2006). For example, in 2018, the acquisition of the biotech company Endocyte and its experimental radiopharmaceutical drug was valued at $2.1 billion, which can be compared to Geely's $1.8 billion acquisition of the Swedish car manufacturer Volvo Cars in the year 2010 (Klesty, 2010; Pagliarulo, 2018).

However, it is worth noting that the financial performance of innovation does not necessarily have a long-term correlation with the amount of money and resources spent on innovation efforts. Instead, what matters is how companies use their means and other resources to create products and services that connect with their customers (Jaruzelski et al., 2013). Therefore, the size of the R&D investments is not of greatest interest in the long-term but rather the productivity of the investments. The R&D productivity puts the hefty investments in R&D that pharmaceutical companies have in relation to its outcome and gives a measurement of how well they can utilize their means and resources.

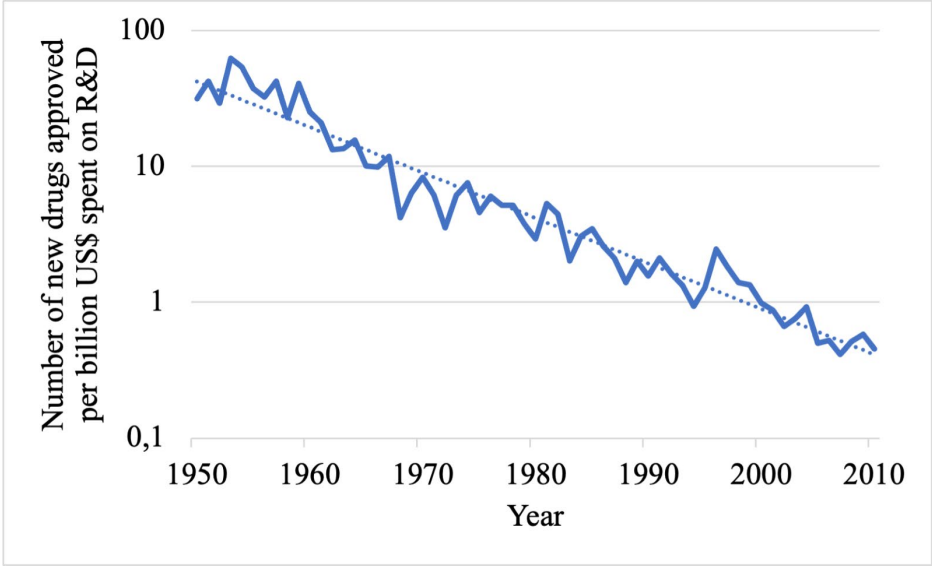
Moreover, the stakes are higher in pharma than in other industries as pharmaceutical companies spend a remarkably higher proportion of their revenues on innovation, namely 11.6 % (Pwc, 2013), compared to other companies where the overall average is 8.6 % (Pwc, 2013). At the same time, 14 % of their revenues come from new products and services when the overall average for the top innovators is 25 % (Pwc, 2013). In a, perhaps telling, study of R&D spending by Booz & Co presented by Jaruzelski et al. (2013), there were seven pharma companies on the list of the top 20 R&D spenders, however, no pharma companies were found on their list of top 10 innovators.

In the past 70 years, considerable advancements have been made in both technology and management. The pharmaceutical industry poses no exception, with breakthroughs ranging from the development of ultra-high-throughput screening (allowing for the quick testing of millions of candidate drugs against an identified medical target) to the fundamental transformations in the knowledge of disease biology following the so-called 'omics'-revolution (i.e., relating to genomics, proteomics, metabolomics, et cetera) (Cook et al., 2014). However, while one could have expected the decades of continuous advancements to translate into a prosperous era of drug development, the fact is that pharmaceutical R&D productivity steadily decreased from 1950 to 2010 (Scannell et al., 2012). During this time, development costs skyrocketed while the pace of drug development remained relatively unchanged, causing a

well-discussed ‘productivity crisis’ (Cook et al., 2014; Munos, 2009; Pammolli et al., 2011; Paul et al., 2010; Scannell et al., 2012). The number of approved pharmaceuticals per billion dollars spent on R&D has halved approximately every nine years, resulting in current-day productivity at only about 1.25% of that of the 1950s, as illustrated in Figure 1 (Mahlich et al., 2021). This 70-year-old trend of exponentially decreasing productivity, referred to as the 70-year-old disease in the title, has been named Eroom’s law; Moore's law for the exponential growth of transistors on a microchip spelled in reverse (Scannell et al., 2012).

Figure 1

Showing the exponential decrease in pharmaceutical R&D productivity referred to as Eroom’s law.



Note. The number of approved drugs refers to approvals by the U.S Food and Drug Administration (FDA). Source: (Nosengo, 2016).

Such decay of productivity poses a serious threat to an industry based on innovation, Mahlich et al. (2021) argue, claiming it puts the entire business model of the pharmaceutical industry at risk. Paul et al. (2010) shares this sentiment, stating: “Without a substantial increase in R&D productivity, the pharmaceutical industry’s survival (let alone its continued growth prospects), at least in its current form, is in great jeopardy” (p. 213).

Moreover, Eroom's law may cause collateral damage that extends beyond the pharmaceutical industry. If the development costs of new pharmaceuticals continue to grow exponentially, either drug prices will follow or the incentives for developing new therapeutic agents must be expected to decrease as stakeholders increasingly value dividends over R&D investments

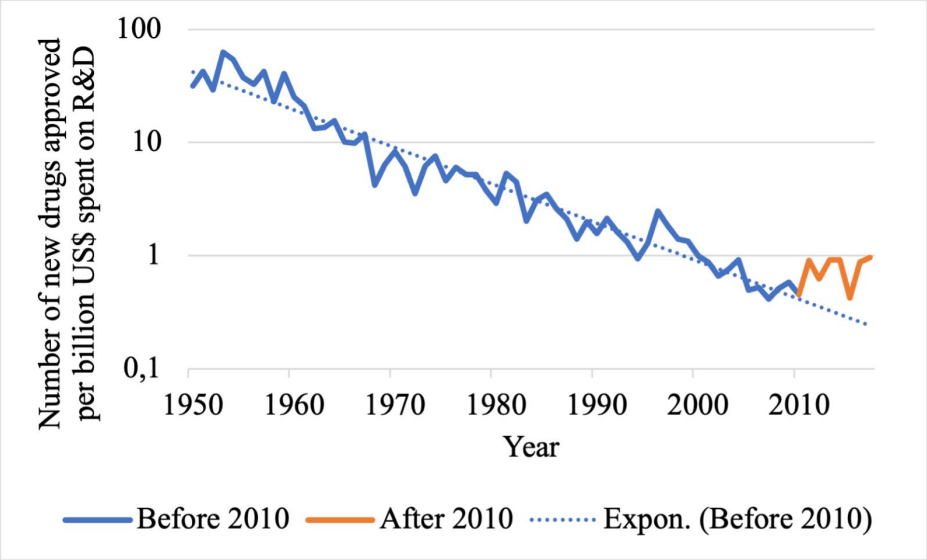
(Scannell et al., 2012). Consequently, the availability of new pharmaceuticals may come to decrease over time, either through diminishing research efforts or escalating drug prices, putting patients and healthcare systems everywhere at risk.

1.1 Problem discussion

While Eroom's law has characterized pharmaceutical R&D since the 1950s and, according to some, has been posing an existential threat to the industry, recent findings show that the trend line has been broken and a turnaround in R&D productivity is ongoing as of 2010, as illustrated in Figure 2 (Ringel et al., 2020). These findings also appear somewhat metric independent, with Pammolli et al. (2020) also reaching a conclusion about increasing R&D productivity since 2010 based on a study of declining attrition rates in drug development, indicating a higher percentage of drugs reaching the market.

Figure 2

The number of new drugs approved per billion dollars spent on R&D.



Note. The number of approved drugs refers to approvals by the U.S Food and Drug Administration (FDA). Source: (Ringel et al., 2020).

Admittedly, these results have been subject to some uncertainty, with Gold (2021) claiming that as Pammolli et al. (2020) measure productivity indirectly through attrition rate, the findings could also be explained by regulatory changes instead of real productivity gain. However, such criticism relates more to the cause of the turnaround than its financial

implications and provided the gloomy outlook for the pharmaceutical industry in the case of a continuation of Eroom's law, the importance of these findings can hardly be understated.

A partial explanation for the turnaround can, according to Ringel et al. (2020), be found in better available information, better utilization of this data, and the emergence of price-insensitive markets with high regulatory risk tolerance, with Scannell (2020) highlighting target oncology and orphan drugs as examples of such insensitive markets. Pammolli et al. (2020), on the other hand, identify how the productivity increase also coincides with an increased industry focus on 'high uncertainty/high potential reward' indications, quicker discontinuations of projects, and novel mechanism of actions, citing these as possible drivers of the trend.

However, despite the significance of these findings, it has yet to be fully understood what changes in the industry and working methods of industry actors the turnaround can be ascribed to. Ringexl et al. (2020) emphasize that the findings only constitute a partial explanation to the turnaround:

> "The data presented in this article support the hypothesis that there has been a turnaround in pharma R&D and that it can be ascribed at least in part to the availability of better information and improvements in the use of that information." (Ringel et al., 2020, p. 834)

Additionally, previous research is mainly based on quantitative reasoning and the qualitative research that has been done is to some degree based on personal interpretations. Moreover, the extent to which the partial explanation mirrors the experience and actions of actors within the industry is unclear.

Besides, Ringel et al. (2020) reason that the underlying factors driving Eroom's law persist and may result in a future return of decreasing productivity in the industry. Similarly, Pammolli et al. (2020) state: "How much of the improvement in R&D productivity that we documented is structural and how much is transient is an important question for future research?" (Pammolli et al., 2020, p. 13). The quote highlights the need to understand if the effects of the underlying factors are enduring or not, which in turn is important knowledge for allowing the industry to work towards maintaining the positive trend as described by Ringel et al. (2020) and Pammolli et al. (2020), as well as to ensure continued resistance to the underlying factors of Eroom's law. However, in order to analyze if the effects are enduring or not, the underlying factors must first to be mapped out.

1.2 Purpose

The purpose of this study is to explore the factors underlying the turnaround in pharmaceutical R&D productivity for the past decade.

1.3 Research question

Since there to some degree already has been a scientific discussion regarding Eroom's law and its underlying factors, previous literature serves as the point of departure in the study. The first research question, therefore, aims to provide this foundation for further research by compiling and clarifying previous literature.

> *RQ1: What does previous literature say are the underlying factors for increasing R&D productivity?*

As stated earlier, previous literature seems to provide a partial explanation of the underlying factors and relies heavily on quantitative approaches for argumentation. We believe that a qualitative approach that relies more on verdicts and perceptions from industry experts can help pinpoint the missing pieces and hopefully complement earlier partial explanations and lead the way to a fuller picture. Regardless, stronger support of already established claims can be confirmed and thereby increase the reliability of existing evidence. With our background, association to Chalmers, closeness to AstraZeneca as one of the biggest actors in the industry, and coupled with the biotech hub atmosphere in Gothenburg that follows from that, a Swedish perspective is a natural orientation of the study. Thus, the second research question aims to add further to the tree of knowledge through interviews with Swedish industry experts.

> *RQ2: What do industry experts in Sweden say are the underlying factors for increasing R&D productivity?*

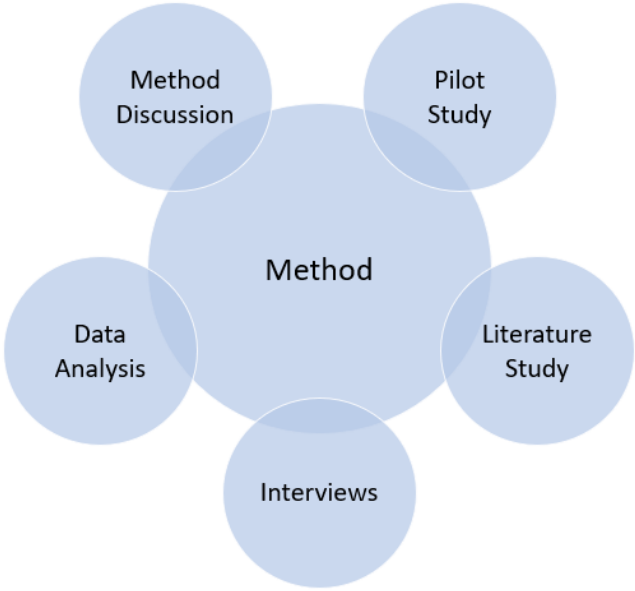
To fully resolve RQ1 and RQ2, they must be looked at from various perspectives. These perspectives include changes within pharmaceutical companies, changes in the pharmaceutical industry landscape, and changes relating to technological and managerial advancements. Furthermore, the findings in the previous literature can help to contextualize the statements of the interviewees, help validate what they say, and add additional perspectives to the analysis.

2. Method

This chapter presents the method used in this study, which is divided into subsections: a pilot study, a literature study, interviews, and data analysis. This is followed by a critical discussion on the choice of method. Figure 3 illustrates these parts in a schematic picture. These parts have been chosen to enable the research design to identify and analyze the underlying factors to the turnaround in R&D productivity.

Figure 3

A schematic illustration of the method essentials.



In the pilot study, information was gathered to gain the knowledge required to carry out the study and ensure its viability. The information gathered also laid the foundation for the interview questions and the literature study, that in turn made up the data for this study. The data analysis of the interviews was performed according to the Systematic Text Condensation (STC) method developed by Malterud (2012), where all the information was ordered from chaos to descriptions and concepts. All parts of the method have not been conducted linearly since new knowledge has been added along the way that needed further investigation. Also, throughout this study, close contact with a collaborative partner within the industry has been established, henceforth referred to as the industry supervisor.

2.1 Research Design and Methodological Perspective

This bachelor thesis has a qualitative research approach, which allows for an analysis of vaguely structured data, such as interviews with open-ended answers, where the results are subjectively interpreted with a high degree of caution (Blomqvist & Hallin, 2015).

Furthermore, this study has an explorative objective. According to Ellram (1996), exploratory research answers questions such as “why” or “how” something is happening or being done. This relates well to the objective of this study which is to explore what factors that underlie the turnaround in R&D productivity, in other words to find out why this turnaround in productivity has happened.

The methodological perspective used in this report is the abductive approach. Reichertz (2010) describes the abductive approach as a combination of induction and deduction. An inductive approach is used frequently in qualitative studies, where investigations of reality are analyzed and generalized within a theoretical framework (Thomas, 2006). Furthermore, this enables conclusions to be drawn from the gathered data. On the other hand, Thomas (2006), says that a deductive approach is the opposite, i.e., through predefined hypotheses conduct studies to confirm or falsify these hypotheses. This study is based on the existing theory combined with experience and knowledge from the respondents, which makes it an abductive approach.

2.2 Pilot Study

At first, this study had a different focus, with a different purpose and other research questions. The initial purpose was to map out how the return on investment compare in drug development projects for repurposed drugs and first-in-class drugs. Data was collected in an iterative way where discussions and interviews with the industry supervisor were combined with literature searches. After some time, the initial purpose of the study was deemed unattainable with the resources given, and a new approach was needed. Therefore, the data collection for the initial purpose was transformed into a pilot study which laid the foundation for the final version of the study.

The pilot study was important to acquire the knowledge required to carry out the study and to ensure that the study was viable, from a thesis perspective. To ensure the viability of the final version of the study, theory and information regarding R&D productivity, drug discovery, regulations, and the pharmaceutical industry were further processed through both literature searches and additional discussions with the industry supervisor. This resulted in a good insight into the industry and laid the foundation for the future parts of the study: the literature study, the interviews, and the analysis.

From the pilot study, a few significant conclusions could be drawn. Firstly, quantitative data regarding the value of a drug in different clinical phases is difficult to obtain, and therefore the

final version of this study focused on qualitative research questions. Secondly, a pharmaceutical company does not necessarily choose between developing repurposed drugs or first-in-class drugs. Rather, they have a pipeline with both. This fact made the initial purpose of the study less accurate. Thirdly, when researching for the first project it often resulted in references to the productivity issues and a problem called Eroom's law. This then became the focus of the final version of the study.

2.3 Literature Study

A literature study was performed, and according to Snyder (2019), it is useful when the aim is to provide an overview of certain research problems. Since the aim of this study is to explore the underlying factors of the turnaround in R&D productivity in the pharmaceutical industry for the past decade, the literature study presents the main problems and factors that affect R&D productivity according to previous studies. Furthermore, R&D productivity is dependent on different variables like regulations, the discovery of new drugs, organizational structures, and the scientific understanding, and these were therefore the focal points of the study. Additionally, the literature study also helps to contextualize the statements of the interviewees, it helps validate what they say, and the literature study adds additional perspectives to the analysis.

The literature study was conducted through semi-systematic searches in databases such as Scopus and Google Scholar. According to Snyder (2019), this is the preferred way when a fully systematic review is not possible due to the topic being conceptualized differently and studied by various groups of researchers.

From the pilot study the turnaround of Eroom's Law was deemed central to the study, and therefore the literature study had its take-off point in widely cited articles that describe Eroom's law and the turnaround. One example of a central article is "Breaking Eroom's Law" by Ringel et al. (2020) published in Nature Reviews: drug discovery, that statistically describes the R&D productivity turnaround. From this article, keywords were identified and explored in databases. Furthermore, the research was expanded into articles that had cited the Ringel et al. (2020) article, and articles that were cited by Ringel et al. (2020). This resulted in a snow-ball-generated set of relevant articles. Other articles that were deemed central from the pilot study were Pammolli et al. (2020) and Scannell et al. (2012) and keywords and snowball selections were used with those articles as starting points too.

Relevant keywords that then served as a foundation for the literature study were the following: "Clinical trial", "drug discovery", "attrition rate", "innovation", "probability of success", "regulation", "M&A", "digital", "indication", "scientific understanding", and "organization". These keywords were used in different combinations and together with words such as "R&D productivity", "Eroom's Law", "turnaround", "pharmaceutical industry", "improve", "impact on", "underlying factor" and "effect", to get a relevant context.

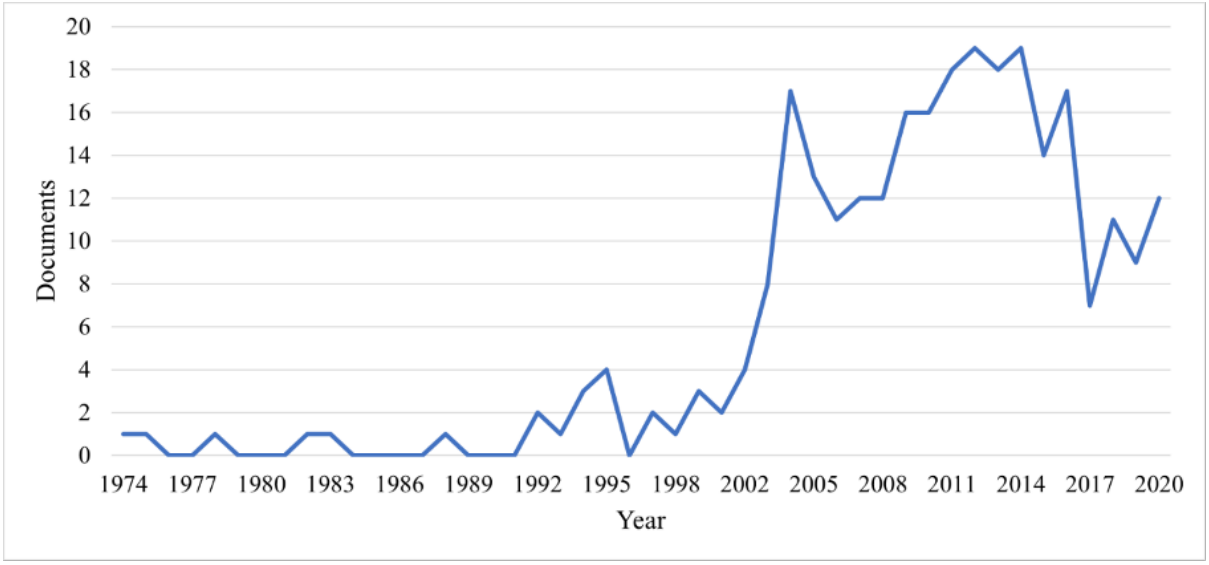
In addition to this semi-structured approach, conversations with people within the industry yielded some additional articles. When the most relevant articles were found, the key reasonings were identified and categorized, which enabled analysis and comparison with the responses of the interviewees. Furthermore, some quantitative data that complements and contextualizes the statements of the articles for the literature study was generated from organizations providing statistics, such as LIF (2021).

2.3.1 Analysis of Scopus database results

Since the literature review is of essence to this study, it is important to analyze the search results of the primary database Scopus and the sources that were used. The purpose is to improve the understanding of the scope of the literature study and the relevance of the topic, as well as to show the systematic aspect of the literature study. The Scopus analysis presented in Figure 4 shows how the topic has gained traction since the start of the century.

Figure 4

Document per year for the search term "R&D productivity pharmaceutical industry" in the Scopus database.



Note. The authors own analysis based on data retrieved from Scopus (2021).

Between 1974 and 2020, there has been 277 articles in total when searching for "R&D productivity pharmaceutical industry", which is a key phrase. Table 1 shows how many articles

that appear when searching within those 277 for each identified keyword specified in section 2.3.

Table 1

The number of results for the search term "R&D productivity pharmaceutical industry + keyword" in the Scopus database.

Keyword	Number of results	Keyword	Number of results
Clinical trial	73	M&A	227
Drug discovery	185	Digital	11
Attrition rate	35	Indication	17
Innovation	197	Scientific understanding	19
Probability of success	7	Organization	133
Regulation	36		

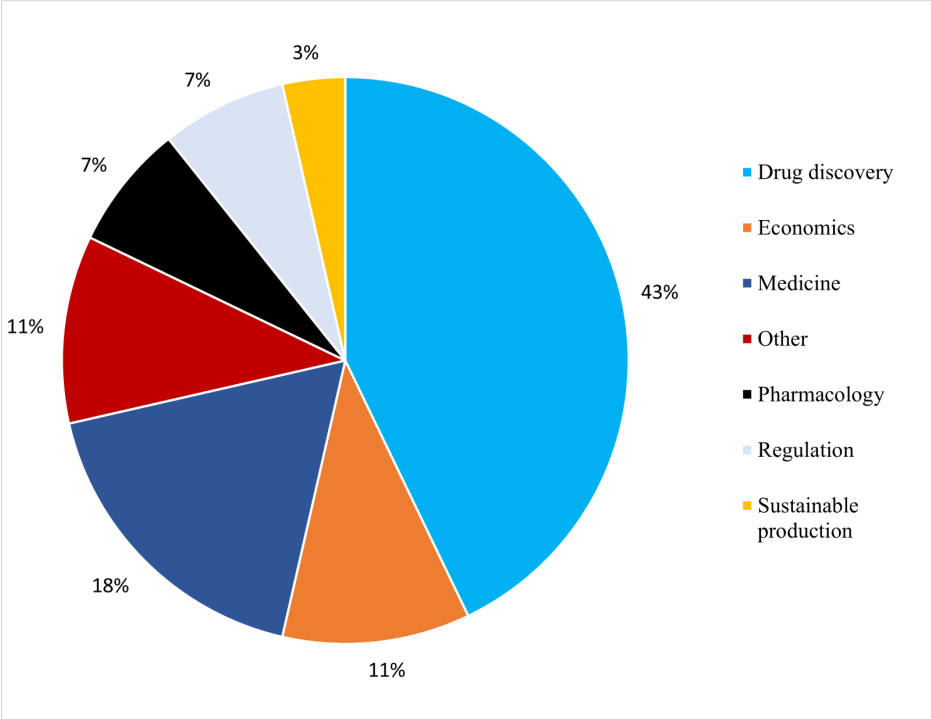
Note. The authors own analysis based on data retrieved from Scopus (2021).

Worth to mention is that the Scopus analysis above highlights only one keyword combination, however, when conducting the study, the keywords have been combined in multiple ways. When studying Table 1, it can be noted that some keywords appear more frequently than others, for example "M&A" compared with "digital". This could indicate that the role of M&A has been more widely explored compared to the role of digital technologies. However, it could also be the result of researchers using other terminology or that the term "digital" is more frequently found in other keyword combinations.

Once again it is important to illuminate that not all sources of the literature study were chosen through a keyword search, but instead some were chosen through a snowball-generation. These two together make up the semi-systematic literature search of the report.

Figure 5

Diagram showing the share of articles used as sources in the literature study that come from journals of different categories.



Note. The "Other" category is primarily constituting of consultancy articles.

Figure 5 highlights that there has been a relevant selection of journals in the literature study that all contribute to the topic of R&D productivity from different, yet still relevant, perspectives. For example, 43% of articles came from journals whose main focus is drug discovery. Example of journals in the category "drug discovery" are Nature Reviews Drug Discovery and Drug Discovery Today.

Although each journal has a specific focus such as drug discovery, the range of articles within that category is still wide. For example, both "Trends in clinical success rates and therapeutic focus" by Dowden and Munro (2019) and "Impact of a five-dimensional framework on R&D productivity at AstraZeneca" by Morgan et al. (2018) can be found in the Nature Reviews Drug Discovery. This shows that although the focus is on drug discovery both managerial factors and statistics on success rates are relevant to drug discovery.

2.4 Interviews

Interviews are often used to collect rich information, on opinions and knowledge, from a small number of people (Virginia Tech, 2018). Additionally, interviews are one of the most effective methods for data gathering in qualitative research and they enable a deeper understanding and exploration of the respondent's opinion, behavior, and experience (Virginia Tech, 2018).

For this study, it was important that the qualitative data collected gave an in-depth description and explanation of the underlying factors to R&D productivity, and what could have caused the R&D turnaround. Because of the need to gain a deep level of understanding, interviews were especially suitable due to the ability to effectively explore the expert respondents' answers and because they give a high degree of descriptive and explanative character.

2.4.1 Design and Conduct of the interviews

In this study, a semi-structured interview method was chosen, which enables for both closed- and open-ended questions, that were followed up by how or why questions. Structuring the interviews accordingly is preferable when qualitative data are being collected (Adams, 2015). By allowing for follow-up questions, the interviewer could direct the discussion and dig deeper into the most interesting subjects. Using this structure, the interviews became more like conversations rather than a formal hearing, which led to a relaxed atmosphere. Thereby, the set-up caused the respondents to feel more comfortable and the likelihood of receiving answers of high-quality was increased (Virginia Tech, 2018).

The preparatory process consisted of finding suitable companies and persons to make contact with. This was done through e-mail or via telephone where the purpose and a short background to this study were presented. Once contact was established, some of the overarching questions were sent to the respondents to make sure they were prepared for the interview. These questions can be found in appendices A and B. However, as the respondents had varying backgrounds, emphasis was put on the aspects that was most relevant to each individual respondent.

Due to the ongoing pandemic of Covid-19, all the interviews were held online via video meetings, e.g., Zoom, Google Meet, or Microsoft Teams. Between three and six members were present at each interview which allowed for multiple perspectives on the follow-up questions and helped make the interview as valuable as possible.

2.4.2 Interview Respondents

Hennink et al. (2016) suggest that nine qualitative interviews can be enough to get an understanding of trends and a general depletion of possible responses from respondents. However, to get a deeper understanding, Hennink et al. (2016) say that 16 to 24 interviews need to be done. The authors distinguish these two levels with "having heard everything"

versus “having understood everything”. To say that between 9 and 24 interviews are enough to having understood everything is a bold statement, since the number of interviews depends on the duration of the interviews, the interviewer's skill, and the respondents (Saunders et al., 2018). Therefore, another factor considered more important when deciding the number of interviews is the data saturation. Saunders et al. (2018) state data saturation as: “In interviews, when the researcher begins to hear the same comments again and again, data saturation is being reached . . . it is then time to stop” (p. 1896). In this study, this phenomenon was observed after ten interviews. The marginal value that was added for the following interviews declined rapidly, and input given in interviews eleven and twelve did not add as much value as the previous ones. Moreover, the respondents gave comments that already had been picked up earlier. Therefore, twelve interviews were considered enough, as found in Table 2 below.

The interviews were held with experts within the industry such as employees at big pharmaceutical companies, smaller biotech companies, regulatory agencies, and industry organizations within Sweden. The respondents and companies were chosen to obtain inputs with varying perspectives of the industry, entailing a holistic picture of the R&D productivity. To get this broad sample size, searches on the web and discussions with the industry supervisor were conducted in addition to personal contacts that the authors already had. Furthermore, after each interview, the respondents were asked if they knew other persons that could contribute to the study, i.e., snowball sampling was conducted which generated additional interviews. It is important to note that the respondents’ answers are given in a personal persona and not as a representative of their respective company. Also, all the interviews were held in Swedish and then translated to English by the authors. The translation from one language to another can introduce bias to the statements of the interviewees when interpreted by the translator. To ensure all statements were correctly interpreted, the interviewees had the chance to review the translated text and suggest changes.

Table 2

An outline of the interview subjects and their respective company affiliations.

Name	Company	Category	Title	Date of interview (2021)	Duration [min]
Jakob Lindberg	Oncopeptides	Medium-sized company	CSO	30-mar	54
Lena Sjögren	AstraZeneca	Big Pharma	Executive Director	31-mar	44
Sven-Olof Lager	AstraZeneca	Big Pharma	Project Finance Director	31-mar	44
Elisabeth Björk	AstraZeneca	Big Pharma	SVP, Late-stage development	20-apr	47
Niclas Stridsberg	Tandvårds- och läkemedelsförmånsverket	Regulatory agency	Senior Analyst	31-mar	47
Dag Larsson	LIF - de Forskande Läkemedelsföretagen	Industry organization	Senior Policy Manager	30-mar	48
Christian Sonesson	Egetis Therapeutics	Biotech company	VP Product strategy and Development	31-mar	77
Christian Pitulia	Cellink	Medium-sized company	Product Development Manager	31-mar	30
Anna Törner	SDS Life Science, SDS Medteq	Regulatory affairs consultant	Business Development Manager	23-apr	53
Jan Nilsson	Combigene	Biotech company	CEO	16-apr	57
Yilmaz Mahshid	Medivir	Biotech company	CEO	20-apr	60
Johannes Hulthe	Antaros Medical	Medium-sized company	CEO	21-apr	48

2.5 Analysis of the interviews

To analyze the interviews systematically, they have all been transcribed using the AI tool Azure from Microsoft. After the AI had transcribed the interviews, they were read thoroughly and corrected by the authors of this study. The findings from the transcriptions were then

categorized according to the theory below and compared and contextualized with the findings from the literature study.

The data analysis has its foundation in the Systematic Text Condensation developed by Malterud (2012) and is often used in qualitative studies, which is strengthened by a Google Scholar search on "Systematic Text Condensation" which gave 231 000 results, e.g., Contextual factors influencing the success of global product development by Sbernini et al. (2018). The article by Sbernini et al. (2018) uses empirical data in order to identify relevant factors to the global product development. This is similar to the purpose of this study which is to identify factors that underlie R&D productivity, through interview data. This similarity further supports that STC is a relevant method.

When using STC the information gathered should be processed through four parts:

1. Total impression – from chaos to themes.
2. Identifying and sorting meaning units – from themes to codes.
3. Conclusion – from code to meaning.
4. Synthesizing – from condensation to descriptions and concepts.

Malterud (2012) states that the first thing to do is to create an overview of the gathered data by creating overarching themes. The next step is, according to Malterud (2012), to identify, clarify, and organize all the elements (or meaning units) that can be connected to the study's research questions. For example, a meaning unit can be a statement by an interviewee. In this step, Malterud (2012) says that it is better to include more information than necessary to minimize the risk of excluding anything relevant this early in the analysis. Once the meaning units were identified, they were connected to the themes created earlier (Malterud, 2012). Furthermore, Malterud (2012) states that this way of coding the meaning units to the themes is done to facilitate findings of patterns within the gathered data which is necessary to be able to perform the last step. The last step is to find descriptions and concepts in the vast amount of information that is collected to identify, formulate and discuss the results (Malterud, 2012).

According to this theory, the respondent's answers were categorized into the themes found in Table 3. Each theme was then analyzed and compiled into condensed information highlighting the factors that affect R&D productivity.

Table 3

The main categories for analysis derived from the interviews.

Increased scientific understanding & its impact on drug development
Externalization of R&D
The interaction with regulatory agencies
Changes in clinical trials; a shift from cautious to adaptive
The role of digital technology to improve productivity
Managerial efforts to promote productivity

2.6 Method discussion

The following section presents a critical viewpoint on the research design, the quality, and the ethical aspect of the study. In particular, the section identifies potential drawbacks and challenges of a qualitative research design, such as inadequate objectivity, replicability, transparency, and presents actions taken to mitigate their impact.

2.6.1 Criticism against the method

According to Bryman (2011), there are three main concerns regarding a qualitative study:

1. Qualitative research is too subjective.
2. Difficulty to replicate the study.
3. Problems regarding transparency.

Bryman (2011) says that the problem with subjectivity comes from the researcher's unstructured perceptions of what they think is important and how the researchers establish relations with the respondents to get as exhausting answers as possible. Due to this, the information gathered from, e.g., interviews, are interpreted differently from person to person and may be a problem when finalizing the results. These tendencies do, according to Bryman (2011), hinder other researchers from replicating the study. Moreover, Bryman (2011) says, that the researcher’s interests often are one of the main drivers of what is being investigated

which further complicates the problem of replicability. The problem regarding transparency, Bryman (2011) says depends on the lack of information regarding how the study was planned and conducted. The subjectivity, replicability and transparency of a study all play a critical role in assessing a study's validity and reliability (Bryman, 2011).

To minimize the risk of the problems mentioned as critical and facilitate objectivity, the study has been both internally and externally reviewed. On an internal level, the study was divided among the authors and continuously reviewed during the project and in places where uncertainties and contradictions occurred, discussions were held. Moreover, the external review was conducted through review sessions with other Bachelor thesis writers and with input from our industry supervisor and our academic supervisor.

In this study, the twelve interviews with people from different backgrounds in the industry, ranging from small biotech companies to governmental agencies, gave a broad insight into the industry and made the authors question the findings when contradictory statements appeared. The statements from the respondents were also set in comparison with what was stated in the literature and this further helped the authors with the objectivity problem.

The problems regarding transparency and replicability have in this study been addressed through a comprehensive method chapter. Another part that can be discussed is the pilot study. The pilot study is in some way a post-construction that came into use when the first version of the study failed. The pilot study is not a complete pilot study, but it was added since the work performed in the first version to a large extent was useful for the final version. Moreover, another important reason why we choose to include the pilot study is to illustrate the whole work process leading up to the final study.

2.6.2 Ethical considerations

Vetenskapsrådet (2017) highlights that ethics are a fundamental part of scientific research. Therefore, Vetenskapsrådet (2017) has four requirements that should be followed to adhere to ethical standards: the information requirement, the consent requirement, the confidentiality requirement, and the use requirement. These requirements ensure that the researchers academically present their research project, that the respondents have decided out of a free will to participate in the study, that the respondents' information is handled correctly regarding secrecy, and that the information collected is only used for the purpose of the research (Vetenskapsrådet, 2017). The first requirement has been considered throughout this study by using academic writing and a distinct structure of the report that facilitates the understanding of the content. To ensure that the respondents knew what they signed up for, they have all been informed of the purpose of the study during and before the interviews. Also, they have been given the option to be anonymized and allowed to read through the report to see if there are any misconceptions. The collected information has only been used in this study and has not been shared with other parties.

3. Key concepts of the pharmaceutical industry

This chapter will present information that is vital to understand the report. While being fundamental to understand the reasonings in this report, it can be seen as elementary for one with knowledge in the subject. Thus, it is recommended to skim this chapter if you have extensive knowledge of e.g., the pharmaceutical industry, the phases of drug development, regulatory affairs regarding drug developments, costs of drug development, attrition rates, et cetera. However, for the uninitiated, this chapter may prove to be of paramount importance.

3.1 The characteristics of the industry

Pharmaceutical companies are driven to manufacture innovative products, and thus, to spend significant amounts on research and development (Statista, 2020). Therefore, companies operating in the pharmaceutical industry need to provide considerable investments. Apart from money, it takes the pharmaceutical companies a long set of links and a considerable amount of time from the start of development to the resolution into a product. Examples of these links are the laboratory research stage, the pilot production stage, the three phases of clinical trials, the large-scale production stage, the market commercialization, and administration approval process, and product marketing (Creative BioMart, 2013).

From the problem-solving perspective, the pharma industry is also unique in the sense that it requires a generation of several alternative solutions and complex testing (Kuwashima, 2015). This is a combination of characteristics only a few other industries and products share. The result of both these characteristics is that pharma companies need to create many alternatives and perform complicated tests (Kuwashima, 2015). Successful and productive pharma companies balance these two characteristics well and can switch at the appropriate time. A prerequisite for this timing in the switch is good management techniques (Kuwashima, 2015).

Moreover, such a long set of links ensures a higher risk since each link is associated with an investment and risk of failure. Therefore, the pharmaceutical industry is full of risks and is not for the faint-hearted. Despite being risky, the pharmaceutical industry renders lofty revenue on successful projects. With a general payback-time of five years or more (Keeling et al., 2010), pharmaceutical companies can revel in monopolistic markets for several years depending on when the patent was applied for.

Because of high expenditures on research, development, clinical testing, and the fact that new drugs often can be imitated easily, patent protection is of vital importance (Scherer, 2000). Consequently, there is a highly notifiable race to being the first to market in the pharma industry, i.e., there are economies of speed.

In addition to this, the safety and efficacy of new drugs are rigorously regulated in most industrialized nations (Scherer, 2000). In contrast to for example the food industry, the

pharmaceutical industry needs to be far more stringent when it comes to maintaining high standards to ensure strength, quality, and purity of the final products (Wood, 2019).

As a final comment on the pharmaceutical industry, it can also be said that it has a big impact on society. Not least, this can be seen in the wake of the pandemic that Covid-19 has caused. As economies around the world are struggling for their survival, businesses are experiencing losses, and individuals face the challenges of a complete upheaval of lifestyle, pharmaceutical companies taking center stage to battle Covid-19 can see positive growth (Pharmaceutical Technology, 2020).

3.2 Phases of Drug Discovery

Two major agencies are regulating the drug market in the western world, U.S Food and Drug Administration (FDA) and European Medicines Agency (EMA). These two agencies work in similar ways when assessing drugs (EMA, 2019). Even though only FDA is referred to in this text, it can be seen as the industry standard.

The U.S Food & Drug Administration (FDA, 2018) explains that there are five steps within the traditional drug development process; Discovery and Development, Preclinical research, Clinical research, FDA Drug Review, and FDA Post-Market Drug Safety Monitoring. The first step in the process is to find compounds that could work as a new drug, and gather information to see how it fits the drug profile, i.e., to see how it is absorbed, distributed, metabolized, and excreted. Before a new drug can be tested on humans, it needs to go through a preclinical study. The preclinical study aims to secure that the drug is safe to use – thus it is often performed on animals.

After the preclinical study is accepted and safety reviews are done, the company can proceed to clinical trials where the drug is tested on humans. To act by major regulations, all new drugs need to undergo rigorous testing divided into three clinical phases before they can get approved. These phases are designed to protect the public and ensure the drug's efficacy and safety (FDA, 2018). In phase I, the drug is tested on a small and healthy population, often less than 100 people. The aim is to see how the drug interacts with the body, and high precautions are taken to safety. Phase II trials are often the first time the company tests if the drug works against the desired disease. The tested population can be up to a few hundred. In phase III, the company needs to prove that the drug is effective and safe on a large population, often several thousand. After all these stages, the company can try to apply for the drug approval at for example FDA or EMA, depending on which market they want to address, and after this, there is a post-market safety monitoring step. It is a long and costly process from discovery to approval (FDA, 2018).

3.3 Productivity in R&D

The permeating subject in this study is productivity in R&D and therefore it is essential to have an understanding of what it is. To successfully measure the productivity of R&D, it is important to first define what the expected output from the research activities is and then adopt a measurement system that fits the current situation (Karlsson et al., 2004). Examples of outputs are number of innovations, number of patents, number of articles published, number of projects completed, etc. (Coccia, 2001). Inputs can for example be personnel and equipment (Coccia, 2001). Another more general example of an input can be the resources in monetary terms for the development of the drug. The productivity to be measured is then the quotient of output/input.

With this in mind, no general method for measuring or evaluating productivity in R&D is used due to the different objectives for the output for different pharmaceutical companies. However, the point of departure for this study is Eroom's Law which defines productivity as the number of new drugs approved per billion US dollars spent on R&D (Scannell et al., 2012). Thus, this is also the productivity measure used in this study.

3.4 Incentives and regulations in the industry

It takes a large amount of financial capital to develop new medications. According to a recent study by Tufts Center presented by DiMasi et al. (2016), the total R&D cost per approved new drug is estimated to $2,870 billion measured in 2013-dollars. Therefore, additional incentives for pharmaceutical companies than selling their new drugs at competitive prices with a low margin must exist. Otherwise, pharmaceutical companies would not invest in research but would instead wait for another pharmaceutical company to develop and license the drug. The result would be a market failure with merely second-mover advantages as other companies would benefit from the research of another company without having to pay for it. It is important to note that far from all drugs going into clinical trials end up commercially successful. Thus, patents and exclusivities are ways for pharmaceutical companies to recoup the losses from failed drugs (Hayes, 2021). By allowing for patents, meaning that pharmaceutical companies are given a period where prices cannot be regulated by the competition, greater investment research is bolstered and these market failures are prevented (Mahdavi, 2017).

Despite patents incentivizing innovations, too much regulation would stunt innovation (Mahdavi, 2017). Simultaneously, too little regulation can restrict people's access to life-saving medications. Patents can be sold and some companies have the competitive strategy of purchasing licenses. When doing this, a middleman between the inventor and the patient is created and as a consequence, the drug prices are raised. This market, being a byproduct of patent protections, is left unregulated (Mahdavi, 2017).

In addition to this, there are complementary methods to increase incentives for drug development by either extending the patents or by strengthening them. These are called exclusivity periods and may or may not run concurrently with a patent (FDA, 2021b). Three examples of this are: drugs being alternatives to antibiotics that may get a 5-year exclusivity extension, a brand-name drug with a new active moiety can receive a five-year exclusivity, and a brand-name drug with an active ingredient that has been approved before may be awarded a three-year exclusivity if a new way of delivering the active ingredient is proposed (for instance a pill rather than a liquid) (FDA, 2021a).

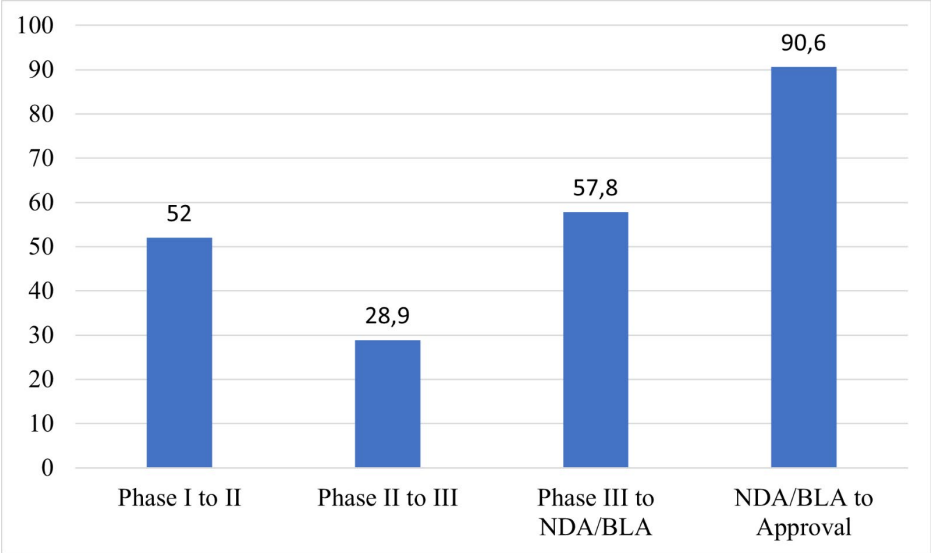
On the other hand, there are ethical concerns regarding the complementary methods to increase incentives for drug development. Pharmaceutical companies often attempt to file for orphan drug status once their patent is about to expire so that their market exclusivity can be extended for an additional seven years. This implicates that pharmaceutical companies use e.g., the Orphan Drug Act to their advantage - receiving orphan drug status for their drug when the medication was not created for that specific illness in mind (Mahdavi, 2017). Consequently, pharmaceutical companies see the possibility of awaiting the expiration of the patent before applying for extended market exclusivity as an orphan drug - all at the expense of the patients that may have to wait for their treatment longer than needed.

3.5 Probability of success and attrition rates

The risk associated with bringing a drug from the preclinical stage to clinical trials, and ultimately to the market, derives from the fact that drugsproject may be terminated due to any number of factors. These can include efficacy, safety, or commercialization concerns (Zhou & Johnson, 2018). The probability of success (POS) is a key input in e.g., valuation models of pharmaceutical assets, and often receive little or no consideration (Zhou & Johnson, 2018). By commitments that increase the probability of success, fewer resources are allocated in projects not resulting in any profit for pharma companies. According to Thomas et al. (2021), and as can be seen in Figure 6, phase II is the largest hurdle in drug development, with just 28.9 % of candidates successfully transitioning from this phase. This can be compared with the POS of 52 % in phase I. Also, different medicinal specialties have disparate POS. For instance, Hematology has a POS of 23.9 % in phase 1, representing a seven-fold increase over the POS of Urology where the POS is 3.6 % (Thomas et al., 2021).

Figure 6

Phase transition success rates from Phase I to approval for all diseases (%).



Note. Source: (Thomas et al., 2021).

A comparison of the success rates for all indications in all clinical phases for 2016 and 2021 shows a decline in the success rate. 63.2 % of all indications were successful when transitioning from phase I to phase II in 2016, whereas only 52.0 % of all indications were successful in 2021 (Thomas et al., 2021). The same pattern can be observed in phases II and III. However, the success rate when transitioning from NDA to approval increased from 85.3 % in 2016 to 90.6 % in 2021 (Thomas et al., 2021).

The attrition rate within the pharmaceutical industry shows how many projects or drugs fail before being able to reach the market. This rate equals 1–POS and is often referred to in general terms. For pharma companies, there are strong incentives to lower this rate due to the hefty investments in the development of drugs that are made. There is a broad range of attrition rates depending on which medicinal field the drug is developed in, but also in which phase the drug is (Kola & Landis, 2004). In addition, there are many reasons why drugs can fail during clinical trials, such as lack of efficacy, lack of safety, lack of funding, and many other aspects with how to follow guidance and recruitment of patients (Fogel, 2018). The main reason for failure in clinical trials is that drug developers fail to show efficacy. In a study of 640 phase III drugs, 54% of the drugs failed, and 57% of them were because of efficacy issues. One reason for the problem is that patients drop out from the trial, or that the study simply got too few patients, the sample size is too small, also called underpowered clinical trial (Fogel, 2018).

4. Existing research on R&D productivity

This chapter aims to provide the reader with an overview of the notable, previously researched topic of declining pharmaceutical R&D. Additionally, it aims to outline the plausible factors for the trend shift and how they can relate to pharmaceutical productivity, and by doing so, answer RQ1. Chapter 4 also prepares the reader for the topics covered in the interviews and complements the results with an academic perspective.

4.1 A background to the historical decrease of the R&D productivity

This section covers notable, published work relating to the decline of R&D productivity. First, an overview of the four most frequently cited causes of Eroom's law will be presented. Second, this view will be complemented by an organizational perspective on pharmaceutical innovation.

4.1.1 The pharmaceutical R&D landscape

A widely cited four-factor explanation for Eroom's law is that of Scannell et al. (2012), consisting of the 'better than the Beatles' problem, the 'cautious regulator' problem, the 'throw money at it' tendency, and the 'basic research–brute force' bias. Together, they describe an increasingly tough R&D environment unsusceptible to every historical advancement that has affected the industry.

The 'better than the Beatles' problem's name stems from its introduction by Scannell et al. (2012):

> "Imagine how hard it would be to achieve commercial success with new pop songs if any new song had to be better than the Beatles, if the entire Beatles catalog was available for free, and if people did not get bored with old Beatles records." (Scannell et al., 2012, p. 311).

This, Scannell et al. (2012) argue, characterizes the conditions of conducting R&D in the pharmaceutical industry. For any given indication, each drug being developed to address it must be better than all previously existing treatment options to be commercially viable. Moreover, the authors propose the existing repertoire of drugs will eventually run out of patent protection and become extremely cheaply available to the market in the form of generic drugs. As such, the bar of developing a commercially and regulatory viable drug is constantly being elevated.

Importantly, the 'better than the Beatles' problem differs from the 'low-hanging fruit' problem which is observable in many industries with some sort of diminishing returns. While the oil industry over time exhausts the easily extracted oil reserves, leading to an increasing marginal

cost of oil extraction, the number of biologically active molecules is next to infinite and unlikely to ever be exhausted. Additionally, the molecules found so far are not necessarily the 'lowest hanging' ones, but many instead serendipitously discovered. However, while extracted oil is continuously consumed which creates demand for additional oil to be extracted, discovered pharmaceuticals will forever remain available on the market. As such, each new drug will effectively lower the value of all future drugs to be discovered for the same indication. Thus, while the low-hanging fruit' problem argues that the easy-to-pick fruit has been picked, the 'better than the Beatles' problem instead suggests that each fruit picked effectively reduces the value of all fruits left on the tree (Scannell et al., 2012).

Pammolli et al. (2011) also support this claim, by writing that all the easy targets already have been exploited, which raises the bar of R&D incrementally as new drugs reach the market. Furthermore, they highlight another factor that makes R&D more complex over time. As basic science advances, innovation opportunities are emerging, and these ever-growing research opportunities make it harder for the companies to focus their R&D on the "right" target when more areas are available for exploration.

The 'cautious regulator' problem refers to how regulatory control has grown progressively stricter over time (Hall et al., 2018), especially in response to pharmaceutical catastrophes such as the Thalidomide scandal. They note that this, in turn, means that more extensive and complex clinical trials are necessitated to achieve the required statistical evidence of efficacy and safety. With clinical trials being the largest contributing factor to expenses in the pharmaceutical innovation (DiMasi et al., 2016), the 'cautious regulator' problem contributes to Eroom's law by escalating the expenses of bringing a new drug to market. Notably, the 'cautious regulator' problem is partially a consequence of the 'better than the Beatles' problem, Scannell et al. (2012) suggest. As better and better treatment options become available to the market, regulators grow increasingly risk-averse simply because they can afford to do so without significantly jeopardizing patients' access to functional medicine (Scannell et al., 2012). Meanwhile, they argue, in the case of indications with no safe or effective treatment available, higher risk tolerance for hazardous side effects and questionable efficacy must be employed.

Together, both the 'cautious regulator' and the 'better than the Beatles' problem contribute to lowering the expected market value of new pharmaceuticals as well as elevating development costs, through larger and more expensive approval processes as well as lower likelihoods of success in each development phase, for indications which historically have been innovation-intensive. Therefore, these two factors also play an important role in pushing the collective R&D efforts towards rarer, less explored, and more serious diseases with lower price elasticity and higher regulatory risk tolerance (Scannell et al., 2012). However, the 'cautious regulator' problem can also partly benefit large, established pharmaceutical companies as the elevated development costs elevate entry barriers and limit competition (Hall et al., 2018).

The ‘throw money at it’ tendency refers to the inclination of pharmaceutical companies to spend considerable resources on expanding supportive functions such as HR without achieving any significant increases in productivity or innovative capability (Hall et al., 2018). Scannell et al. (2012) consider this to be the result of a poor understanding of what drives ROI as well as the significant first-mover advantages of the intellectual property intensive industry creating a temptation of increasing the available budget in hopes of expediting the time to market. Thus, the authors state, the ‘throw money at it’ tendency contributes to Eroom’s law by increasing development expenditures without notably improving productivity.

The ‘basic research–brute force’ bias refers to an overestimation of how advances in basic science and brute force screening methods, such as high-throughput screening (HTS), impact the likelihood of approval for new molecular entities (Scannell et al., 2012). Since the 1990s, these advancements have caused industrialization of early-stage drug development, with the previous trial-and-error, in-vivo based searches increasingly being substituted for screening for leads against biological targets (Scannell et al., 2012). However, Scannell et al. (2012) explain, while the systemization is measurably more efficient in each stage of drug discovery, the efficiency has not been transferable to the later stages of drug development; the likelihood of success in clinical trials has been the same for small-molecule drugs over the past 50 years. As the largest cost of drug development is the cost of unsuccessful projects, the failure to leverage advancement in basic research and brute force screening methods to ensure the probability of clinical success in pursued candidates in all likelihood also constitutes a failure of breaking the trend of escalating R&D expenses since they continue. Especially, they argue that while brute-force screening methods are undeniably very efficient, the changes in the R&D process they caused may be less efficient than their pre-1990's counterpart. This is a consequence of being prone to suboptimization and with an overly large emphasis on quantifiable, measurable results at the expense of overall quality (Scannell et al., 2012).

These four problems in general, and the ‘better than the Beatles’ problem in particular, Pammolli et al. (2011) argue, have led to a growing amount of research activities focused on developing selective drugs in complex research areas, characterized by a low probability of success. These drugs are difficult to get approved and many projects fail to reach the market, which statistically leads to higher R&D spending per approved drug since the cost of project failures are added to the cost of the projects that reaches success (Pammolli et al., 2011).

Pammolli et al. (2011) continue with the reasoning of fundamental economics, arguing that a higher POS should lead to an incentive to continuously innovate within that area. If sales are kept constant, a higher POS should result in higher expected revenue compared to an area with lower POS. However, a higher POS also attracts more competitors and makes the market more price-sensitive which potentially could lead companies towards areas with lower POS, as the lower level of competition means greater potential rewards upon success (Pammolli et al., 2011). Such reasoning could be a factor driving the decline in pharmaceutical R&D productivity.

FDA (2004) states that the regulatory framework is a key factor to the R&D productivity decline. The pace of how new drugs are developed compared to the pace at which new tools are developed to better assess the safety and effectiveness of these new drugs are not correlated (FDA, 2004). Furthermore, this makes the developers use the tools and concepts from the past to assess the drugs of this time, making the clinical trial process more difficult, time-consuming, and expensive than it could be.

4.1.2 The organizational structure

According to Cuatrecasas (2006), other factors are affecting the decline in R&D productivity than those mentioned above. He states that the decline is caused mainly by corporate policies that discourage innovation in companies. Not only is the decline in R&D productivity dependent on the fact that each new drug effectively lowers the value of all future drugs to be discovered and the regulatory issues, but Cuatrecasas (2006) states that the organizational structure also can be a factor.

In the 1980s, Cuatrecasas (2006) argues, a trend shift took place in pharmaceutical companies. Companies started to grow bigger and modern managers with non or little technical experience entered as high-level executives. The free and relatively open environment in which the research was conducted was uncomfortable for them. Therefore, consultants were hired and suggested structural reshaping and behavioral change based on the knowledge gathered from non-medical companies. These changes made the companies believe they could manage and mandate results with more order, formality, creativity, discipline, and efficiency. However, changes such as these suffocate environments promoting innovation and creativity. Consequently, freedom and flexibility were replaced by a bulky and inflexible organization.

Another aspect driving this development further is the pressure from the shareholders, Cuatrecasas (2006) argues. They want short pay-back times on their investments and therefore chief executive officers have to consider cost-cutting operations instead of focusing on drug development programs that, in the best-case scenario, can yield revenues in a decade. By acquiring other companies, existing sales can be kept up. This trend makes big companies even bigger and stiffer and the environment that fosters innovation and creativity is suffocated to a greater extent.

4.2 The changes relating to the turnaround in R&D productivity

This section describes the shifts that have occurred in the pharmaceutical industry, related to drug research and development. A range of sources on the topics has been used to get a wide understanding of changes to the industry. The section will also describe actions that literature suggests should be taken by the pharmaceutical industry to promote R&D productivity, as well as actions that are the future of drug development.

4.2.1 A focus on other types of drugs

This section describes what type of drugs are developed by the industry, compared to previous years in terms of indication, orphan status, and complexity. The purpose of this is to identify trends in drug development that could be traced back to R&D productivity.

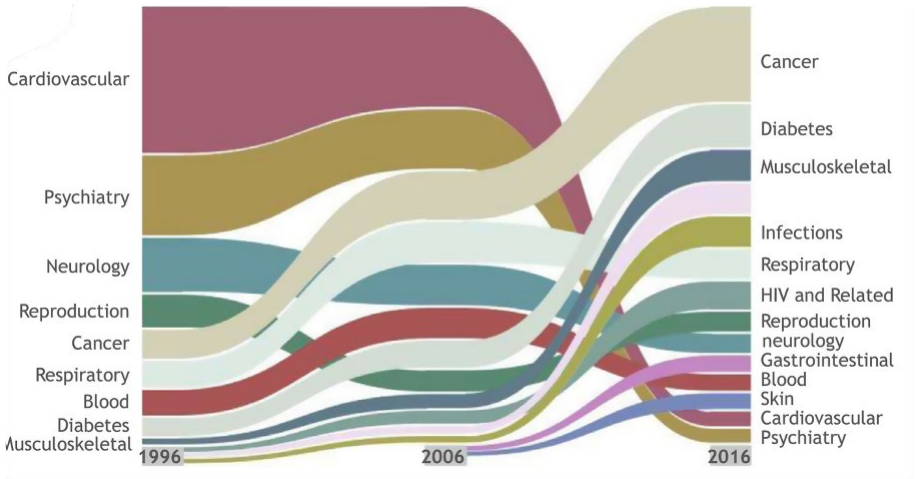
4.2.1.1 Towards oncology

The decrease in pharmaceutical productivity threatens the finances of pharmaceutical companies, which has resulted in a shift in therapeutic areas towards those most profitable (Réda et al., 2020), where oncology drugs generate the largest amount of revenue followed by diabetes (Lee et al., 2019). Cardiovascular disease (CVD) that in 1996 was the most significant therapeutic area in terms of revenue has experienced a sharp decline in revenue and is no longer prioritized by the industry as a whole (Lee et al., 2019).

Van Norman (2017) argues that in 2008, there was a tipping point, from cardiovascular to oncology and central nervous system diseases (CNS). In 1990, there were 13 %, 12 %, and 21 % in clinical trial phase I, II, and III respectively. But in 2012, the number for each phase was 3 %, 3 %, and 7 %. Van Norman (2017) also points out that in 2012, the Breakthrough Therapy Designation Program was approved, allowing for faster approval of drugs that have shown preliminary success, and in 2016, 45 % of all projects in the program were related to oncology, whereas only 2 % were related to CVD.

Figure 7

The share of the total revenue from the pharma industry by year.



Note. Figure available under the Creative Commons Attribution-NonCommercial-NoDerivs License. Source: (Lee et al., 2019).

As can be seen in Figure 7, there has been a drastic shift in what diseases are revenue-generating. Previous blockbusters such as cardiovascular diseases and psychiatry have decreased in revenue-share in favor of diseases such as cancer and diabetes.

Pammolli et al. (2020), further emphasizes the significance of oncology research to the industry. They write that 40 % of ongoing clinical trials in 2018 were related to oncology and that four out of five of the top therapeutic classes in drug development projects fell under the oncology classification. They describe that within oncology, certain classes such as monoclonal antibody neoplastics and immunosuppressants have shown the largest increase, whereas other areas such as antineoplastic and immunomodulating agents have stayed identical. Moreover, oncology research has been a major driver of decreasing attrition rates in early-stage clinical trials. However, the late-stage trials' decreasing attrition rate is mainly due to anti-infection drugs (Pammolli et al., 2020). This shows that oncology research has been significant for the improvement of R&D productivity.

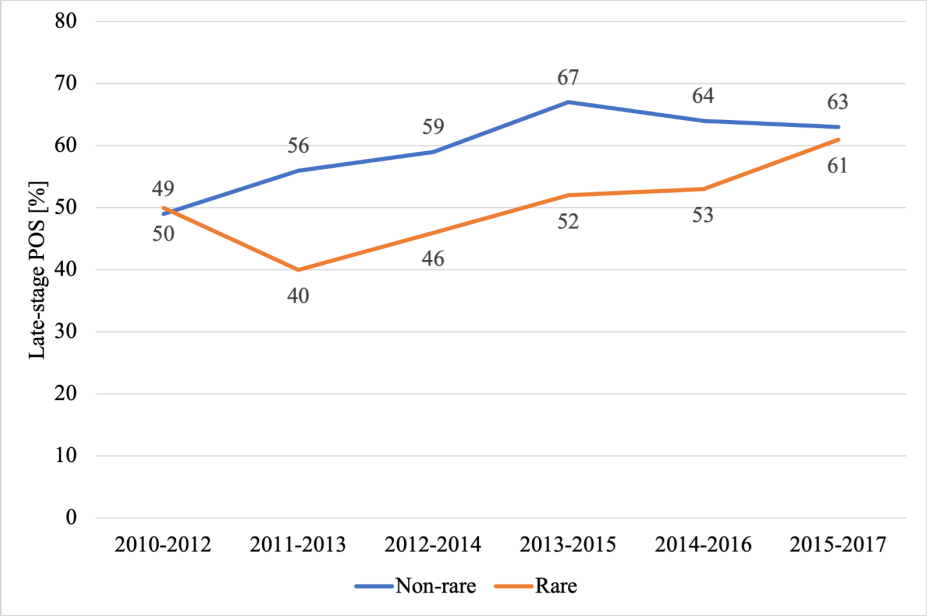
4.2.1.2 Towards orphan drugs for rare diseases

Projects relating to orphan drugs have doubled in frequency between 2000-2009 and 2010-2017 (Pammolli et al., 2020). Similarly, in 2017, 16 % of all drug projects were related to rare diseases, whereas the same number in 2003 only was 3 % (Pammolli et al., 2020). This shows an increased interest in the development of drugs for rare diseases. However, Pammolli et al. (2020) also argue that orphan drug development results in longer and more complex studies, citing a 2.3 % average increase in orphan drug development time, which is significant considering the long period that is usually involved in drug development. According to the authors, this could be due to the complexity of drug development when there are fewer patients involved and the fact that rare diseases often come with a lack of biomarkers for easier testing and analysis of validity.

Dowden and Munro (2019) state that on the other hand, the late-stage probability of success (POS) of rare drugs is increasing and is converging with the late-state POS for drugs targeting non-rare diseases. Pammolli et al. (2020) argue that the phase III attrition rates remain high for orphans compared to non-orphans, relating that to the difficulty in recruiting patients for trials.

Figure 8

How the POS has changed over time for rare and non-rare drugs.



Note. Source: (Dowden & Munro, 2019).

Figure 8 highlights how companies have become better at developing rare drugs in terms of late-stage probability of success. It is worth noting that the data is cut off in 2017 and at that point, the different types of drugs had very similar POS. It is also clear that the POS has improved for both types of drugs.

Dowden and Munro (2019) further mention that almost 25 % of all phase II and III trials consist of rare diseases. They trace this to the increased sub-division of the oncology research area, where breast cancer for example can be further split into different types depending on the genetic mutation. These sub-splits can then by themselves be referred to as rare diseases. This fragmentation coupled with the increase in oncology research as established in section 4.2.2.2, increased awareness of rare diseases, better patient data, and regulatory support such as the Orphan Drug act of 1983 are the leading causes behind the increase in orphan drugs (Dowden & Munro, 2019). Pammolli et al. (2020) argue that rare diseases to a larger extent can avoid the 'better than the Beatles' problem as described in section 4.1 and that they represent a majority of drugs in FDA's fast track programs that allow for faster approval.

Furthermore, 34 drugs representing 58 % of all NDAs approved in 2018 were rare drugs, and 27 of these were developed by smaller biotech companies. (Dowden & Munro, 2019) This will be further expanded upon in section 4.2.2.

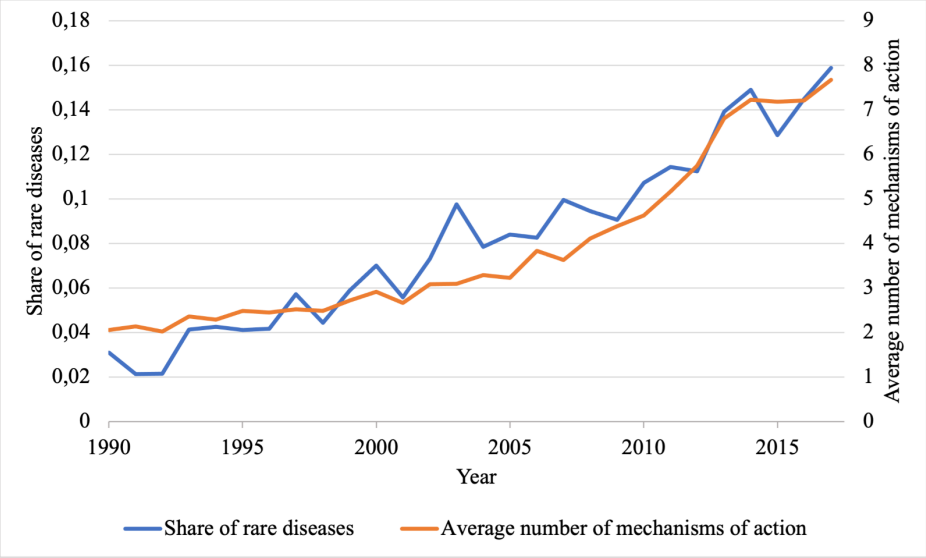
4.2.1.3 Towards greater drug complexity

Pammolli et al. (2020) argue for a paradigm shift in drug complexity that can occur because of an improved scientific understanding of diseases down to a molecular level. One example of this paradigm shift is towards drugs that because of an increased scientific understanding now can have multiple mechanisms of action, as illustrated in Figure 9. Worth noting when studying Figure 9 is how the exponential increase of drug complexity in terms of mechanisms of action took off drastically between 2005 and 2010. Figure 9 also shows that the share of rare diseases has increased during the same period.

This complexity may make drugs more effective, but also more difficult to develop and the time for preclinical design takes longer, and since 2010, there has been a marginal average increase in the duration of the preclinical study (Pammolli et al., 2020). Additionally, Pammolli et al. (2020) add that a large proportion of the advanced drugs are within oncology, which also can be a contributor to the increase in oncology drugs as explained in section 4.2.1.1.

Figure 9

The average number of mechanisms of action of a drug and share of rare diseases over time.



Note. Source: (Pammolli et al., 2020).

Pammolli et al. (2020) also describe how the degree of novelty of approved drugs has shifted over time. By degree of novelty, they mean both in terms of the indication the drug targets, and in terms of what mechanism of action the drug has (Pammolli et al., 2020). The authors concluded that successful projects had a higher median novelty compared to the median

novelty of failed projects, suggesting that novelty of drug projects could be a contributing factor to R&D productivity (Pammolli et al., 2020).

Precision medicines are another important therapeutic method for meeting R&D productivity demands. In 2018, approximately 40 % of all FDA-approved drugs were precision medicines (Malandraki-Miller & Riley, 2021). The term is primarily used to describe medicines that are based on genomics (Dugger et al., 2017). It is precise in terms of that the medicine is developed to target a certain type of genetic condition, for example, a certain genetic mutation in cancer cells (The American Cancer Society, 2020). The increased knowledge in genetic sequencing and the ability to trace the genetic change to a certain disease has allowed for the increased integration of genomics and drug development that has been hyped by the industry for decades (Dugger et al., 2017). As a consequence, disease therapy in general moves away from the "one size fits all" approach of previous treatments to more mutation-specific treatments, implying smaller patient groups (Dugger et al., 2017). Oncology research has been leading the precision medicine area, and this has also driven the development of diagnostics so that the right patient can be combined with the right medicine and the development of new clinical trial designs, see section 4.2.3.

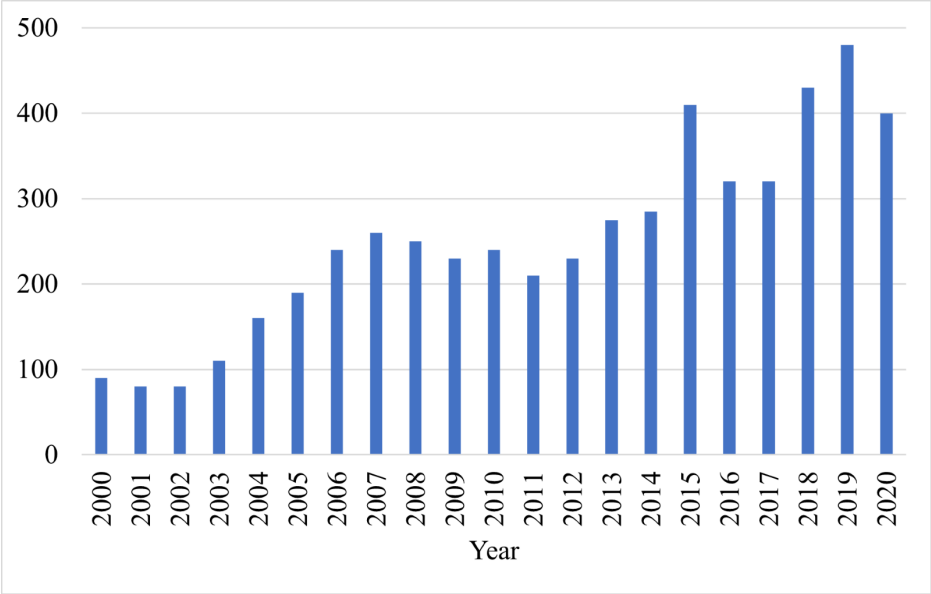
Pammolli et al. (2020) argue that companies are becoming better at identifying relevant patient sets, based on biomarkers. And Pammolli et al. (2020) highlight the significance of precision diagnostic assays in their role in diagnostics and as clinical endpoints. With proper diagnostics, it is easier to determine the success of the drug in the trials. Moreover, Dugger et al. (2017) argue that being able to split up patient groups depending on their genetic condition will result in higher success rates within the smaller populations which is beneficial to everyone involved in terms of both efficacy and costs.

4.2.2 The roles of different actors in the industry

Mergers and acquisitions (M&A) are at an all-time high (prior to the covid-19 pandemic), both in terms of number and monetary value, where the deal count can be seen in Figure 10. The deal count has roughly increased four-fold since the beginning of the century.

Figure 10

The number of M&A deals in the pharmaceutical industry over time.



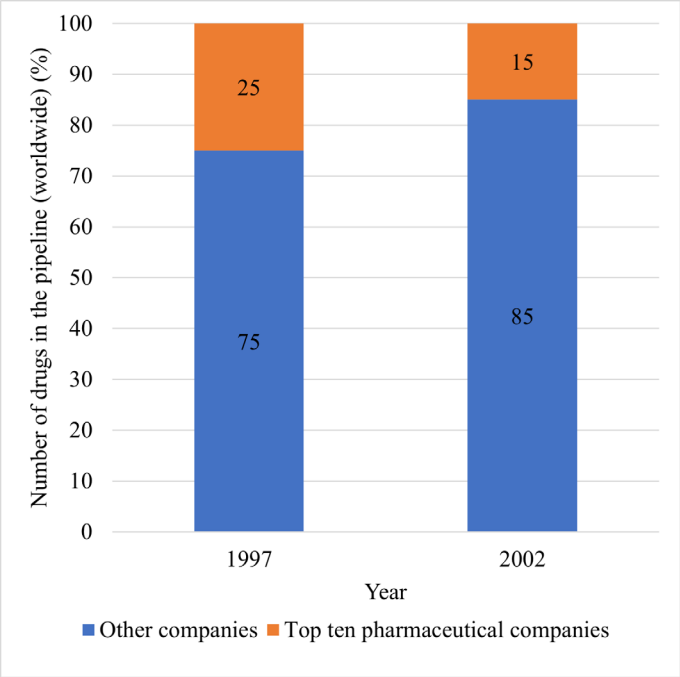
Note. Source: (Ascher et al., 2020).

M&A is common in the industry for three major reasons as outlined by Ascher et al. (2020): they are to source innovation such as digital platforms, to generate economies of scale, and to refine the drug portfolios of the pharmaceutical companies. All of these reasons contribute to R&D productivity, either in terms of increasing drug output, or decreasing costs. However, M&A is not the only way to source innovation from external parties. Other arrangements such as joint ventures, cooperations, and R&D alliances are also possible ways, and further explains that there is a wide range of AI-related activity amongst companies active in the industry (Schuhmacher et al., 2020).

Booth and Zemmel (2004) argue that the M&A trend started around the mark of the 2000s. Around that time, the top ten pharmaceutical companies' share of the total number of drugs in pipelines in the industry started to decrease, as illustrated in Figure 11.

Figure 11

The shares of the drugs in the pipelines around the year 2000.

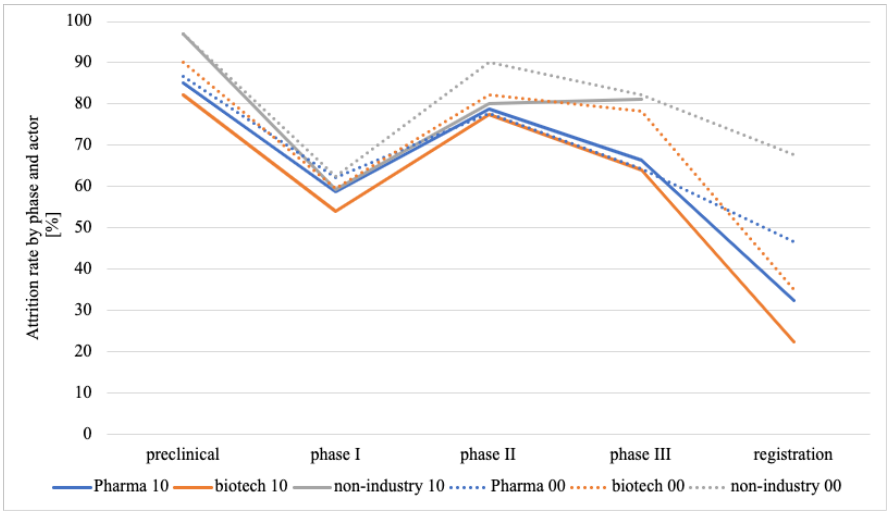


Note. In the year 1997, 100% was equal to 5015 drugs, respectively 5604 drugs in the year 2002. Source: (Pammolli et al., 2020).

Another significant perspective is that of the attrition rates of different industry players which are illustrated in Figure 12 (Pammolli et al., 2020).

Figure 12

The attrition rates across phases for pharma, biotech, and non-industry in 2000-2003 and 2010-2013.

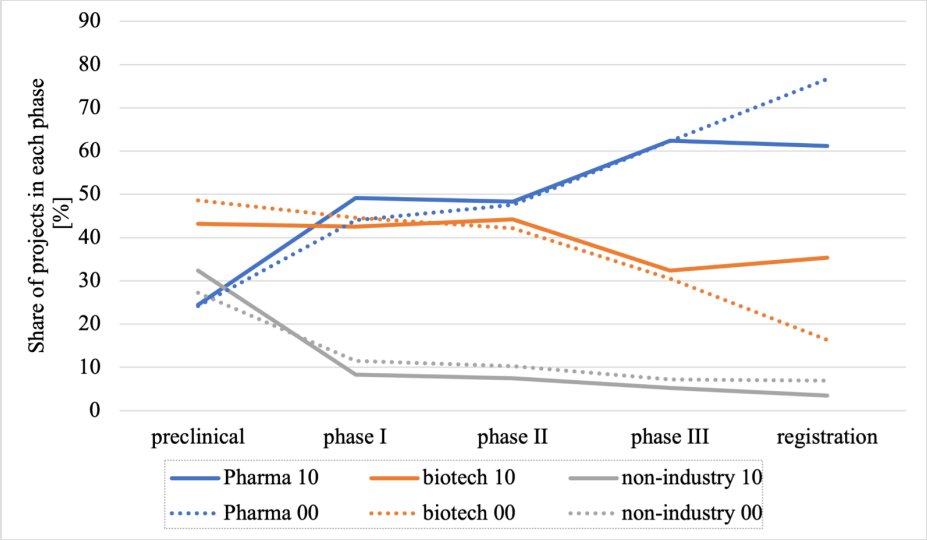


Note. Non-industry did not have data in registration for the period 2010-2013. Source: (Pammolli et al., 2020).

Figure 12 shows that the attrition rate, in general, has decreased compared to the start of the data from the year 2000. Figure 12 also shows that it is a marginal difference between different actors' performance in clinical trials. The changing role of biotech companies is further highlighted in Figure 13 based on data from (Pammolli et al., 2020). Here it can be seen that the major difference lies in the late stages, where pharma and biotech are converging. This implies that an increasing number of biotech companies are also developing and commercializing the drugs, and not just inventing the drug (Pammolli et al., 2020).

Figure 13

The industry actors' share of projects in each phase for 2000-2003 and 2010-2013.



Note. Source: (Pammolli et al., 2020).

Dowden and Munro (2019) mention in their article that 27 of the 34 rare drugs approved in 2018 come from smaller biotech companies. They suggest that due to the orphan status all things are on a smaller scale, for example, trial size, making it easier for small biotech companies to compete with large pharmaceutical companies on this type of drug. This correlates well with Figure 13 that suggests that smaller biotech companies are to a larger extent commercializing their drugs.

Another perspective to take into account is that of Cuatrecasas (2009), who argues that mega-mergers between large pharmaceutical companies in the 2000s are negative for productivity in the long run. This is because of the loss of the intellectual knowledge base and unique research cultures which contributes to decreasing innovation. Cuatrecasas (2009) acknowledges that mega-mergers can contribute to satisfying short-term profitability demands, but that attempts at mega-mergers in the 2000s resulted in the loss of many successful companies such as UpJohn and Searle.

A further significant trend relating to drug development is that of partnerships. For example, the outsourcing of research to clinical research organizations (CRO). To reduce costs, there is a growing number of drug manufacturers that are outsourcing large parts of R&D, mostly to clinical research organizations. In 2011, the outsourced research consisted of 34% of the research whereas that number in 2020 was estimated to be 50% (Statista, 2016). Furthermore, the private-public partnership is another example that can help improve R&D productivity. By combining data, resources, expertise, and ability to execute, new approaches can be taken to

coherently reach the final goal of the ultimate benefit of patients (Laverty et al., 2012). Similarly, the same ideas can be found in innovative regulatory frameworks such as the "Clinical path initiative" that aims to address industry challenges through collaborative effort to create a new generation of performance standards and predictive tools (FDA, 2004).

4.2.3 The method for drug discovery and clinical trial designs

This section first describes a new method for clinical trials that is critical to attrition rates for pharmaceutical companies and then moves on to look at improved discovery processes.

4.2.3.1 Adaptive clinical trial design

Clinical testing is significant to R&D productivity in the pharmaceutical industry. As described in the frame of analysis, high attrition rates are a cost driver and as established by Hartford et al. (2018), the attrition rates of late-stage trials have the largest effect on R&D costs.

With more precise medicines that come with smaller patient populations, it is becoming more difficult to do the typical late-stage trials, with hundreds or thousands of patients (Mahlich et al., 2021), because of difficulties in recruiting and finding patients.

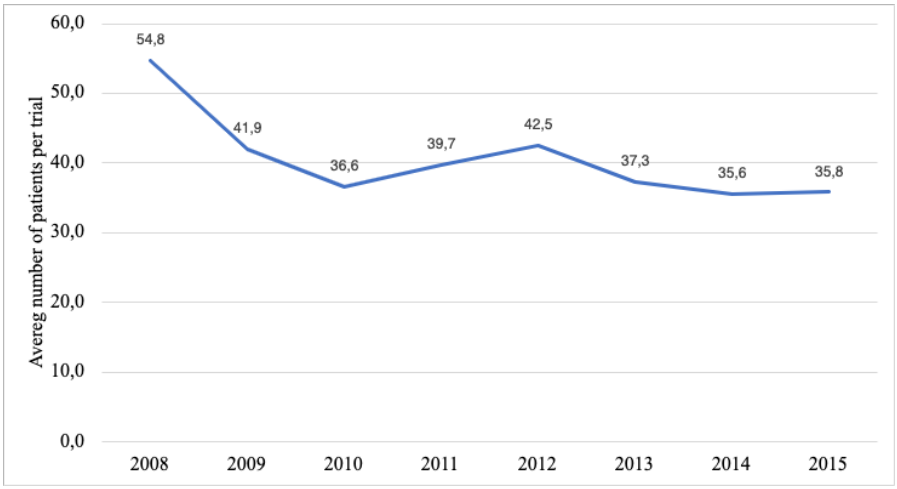
A suggested methodology for improving the clinical trial design is called adaptive clinical trial designs. Research has suggested increased acceptance of the methodology that first surfaced in the 1970s, showing that the method appeared more frequently in the literature between 2012-2016 than between 2008 to 2011 (Hartford et al., 2018). Réda et al. (2020) further mention that the fact that FDA posted guidelines on how to do adaptive design is a success for the methodology. Adaptive design is defined as a clinical trial design that uses accumulated data to modify the ongoing trial (Hartford et al., 2018). One purpose of the adaptive clinical trial designs is to discard ineffective trials sooner, so that resources can be reallocated, and to be ethical by canceling the study early when data shows it does not work. The early stopping of trials when a phase has begun is not allowed in traditional clinical testing (Hartford et al., 2018).

Common adaptations to clinical trial designs that are done following interim analysis of the accumulated data are to stop the phase early, to adapt the patient group based on for example demographics or genetic markers, and to re-estimate the patient group size while maintaining statistical significance and validity of the trial (Hartford et al., 2018; Mahlich et al., 2021). This, Mahlich et al. (2021) argue, allows for avoiding "negative" trial results and unnecessary costs. Mahlich et al. (2021) looked further into how adaptive design decreases attrition in phase III and suggested a low estimate of a cost reduction of 14 % per new drug, contributing to increasing the R&D productivity. Though the adaptive clinical trial design may also come with increased costs for doing complex interim analysis and generating good data (Mahlich et al., 2021), there may also be issues if the data is delayed (Réda et al., 2020).

Adapting the design of clinical trials is also vital in precision medicine, where the target group must be adapted so that all the patients have the same underlying factor causing their disease, for example, the same genetic mutation (Dugger et al., 2017).

Figure 14

The average number of patients per trial.



Note. Source: (LIF, 2021).

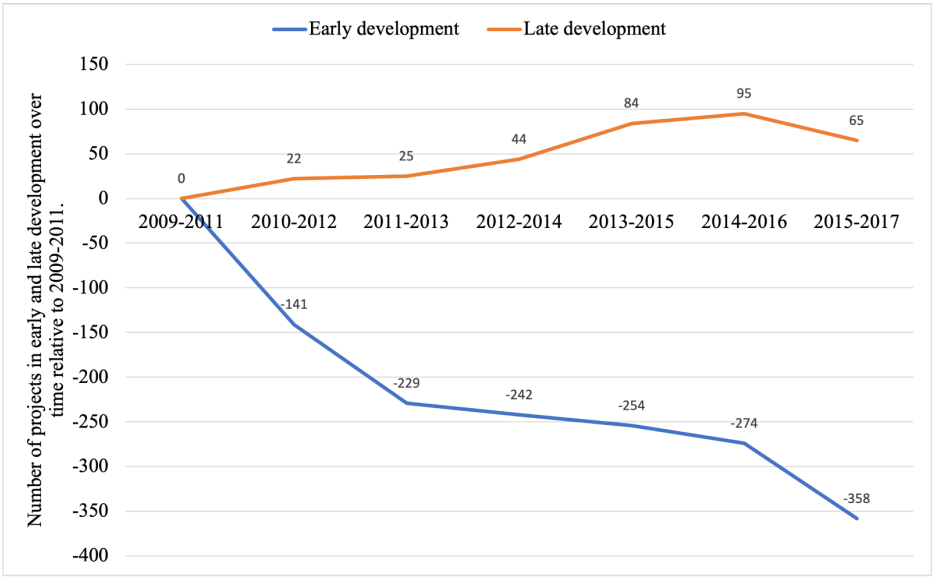
Figure 14 exemplifies how the number of patients on average in Swedish clinical trials has decreased lately, showing how there has already been a shift towards smaller studies in the Swedish pharmaceutical industry.

4.2.3.2 Improved preclinical research and drug discovery processes

In the early 2000s, common methods for drug discovery included the "shots on goal"-approach. Meaning that companies wanted to push as many candidates as possible into clinical trials so that at least one candidate made it through (Dowden & Munro, 2019). This correlates with the 'basic research – brute force' bias as described in section 4.1. Now the trend has shifted, and the companies are becoming more selective in what candidates they move through their pipelines and allocating their resources to (Dowden & Munro, 2019), resulting in a decrease in projects getting into early-stage development as illustrated in Figure 15.

Figure 15

The relative number of projects in the early and late stages of clinical trials, relative to the "0" point in 2009-2011.



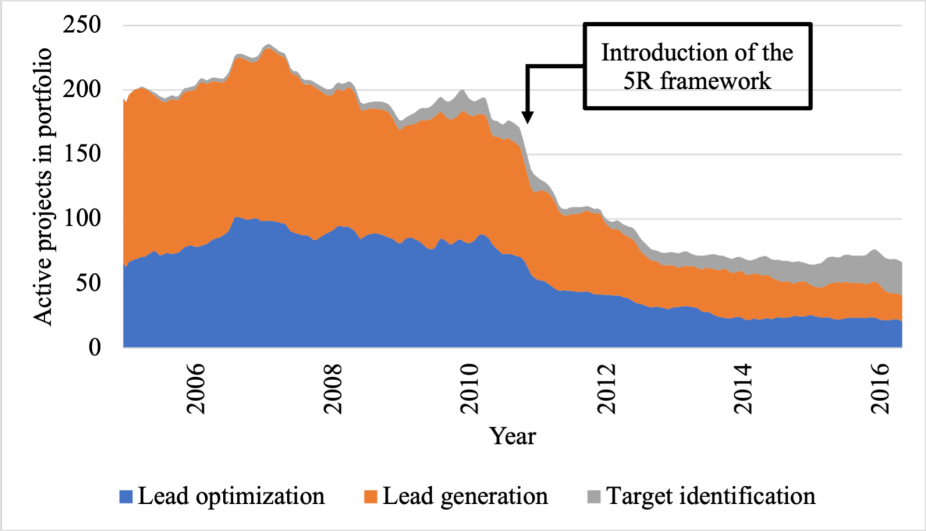
Note. Source: (Dowden & Munro, 2019).

Dowden and Munro (2019) argue the dip in late-stage trials in 2015-2017 could be a consequence of fewer input candidates in phase I in the years prior, and that the POS for the drugs in late-stage is higher now. Assuming they can maintain a similar output, this means there is a decreased attrition rate in late-stage development, which is associated with decreasing costs and therefore increased R&D productivity.

Furthermore, Morgan et al. (2018) describe that AstraZeneca has successfully implemented a framework called "5R" to ensure drug candidates have appropriate qualities before moving into clinical trials. The 5R consisted of having the Right target, Right tissue, Right safety, Right patient, and Right commercial potential. These should be established before any further clinical action is taken (Morgan et al., 2018). AstraZeneca reports the implementation of this framework has drastically decreased the number of ongoing projects aa. The focus of the projects has also shifted, and after the implementation of 5R, a larger portion of the time is spent on target identification as illustrated in Figure 16 (Morgan et al., 2018).

Figure 16

The active preclinical projects of the AstraZeneca pipeline over time, as well as the phase of preclinical development they are in.



Note. Source: (Morgan et al., 2018).

The reported benefits of this included improved success rate in all phases of clinical trials and the costs to reach a clinical "proof of concept" decreased and is now 42 % lower than the industry average (Morgan et al., 2018). Furthermore, they reported a decreased cycle time for preclinical research from 26 to 19 months, attributed to the fact that they work on fewer projects and can focus on those (Morgan et al., 2018).

Pammolli et al. (2020) also argue that a force behind decreasing attrition rates is that there is an increased focus on validation of drugs and drug targets already in preclinical development, which is what AstraZeneca did.

4.2.4 The use of technology

As in every industry, technology has been implemented in the pharmaceutical industry to help improve operational, compliance, clinical, regulatory, and financial performance (Davidson, 2018). However, as brought forth by Mahlich et al. (2021), evidence suggests that new technology has not contributed to increased productivity. This is labeled the Solow paradox, as famously stated by the Economics Nobel laureate Robert Solow in 1987: "You can see the computer age everywhere but in the productivity statistics."

The Solow paradox has been firmly supported in IT-intensive industries with backing from empirical studies that find little proof of increased productivity. Nevertheless, this section aims

to outline some of the most important technology advancements that the industry believes can help improve R&D productivity.

4.2.4.1 Digital information technology

Many different types of digital technologies are currently being used in the pharmaceutical industry to build closer relationships with patients and gather more and better data (Guarita et al, 2021). This data is shuffled back to earlier stages in the development process to help set a proper foundation for the discovery of new drugs. For example, mobile applications can be used to identify new needs and further verify medical symptoms and reactions. Desai et al. (2020) put it clearly:

> "Shifting from traditional paper-based to electronic data-gathering platforms will allow the pharmaceutical industry to collect real-world, real-time, clinically relevant data, capable of informing current and future drug product development, reducing time and cost, and setting foundations for patient-centric drug product design." (Desai et al., 2020, p. 1)

Likewise, new methods for data collection during the early stages of drug development help with development in the later stages. Coupled with advances in data science, open data, and collaboration schemes such as open innovation or crowdsourcing, this is a dealbreaker for the development of new drugs. With clean and well-annotated data situated in open databases, containing information such as genomic data, interaction data, drug-disease associations, clinical trial data, chemical, and drug data, innovation can cultivate the development-cycle back and forth (Thompson & Bentzien, 2020).

4.2.4.2 Blockchain

Blockchain, or distributed ledger technology, brings with it an opportunity to store data securely and transparently. This leads to decreased costs and increased trust for all participants involved. For example, blockchain can be used to protect intellectual property information while at the same time making it accessible for the appropriate parties in a secure way. This fosters cross-collaboration, which previously has been blocked by the established intellectual property systems due to high complexity. Ensuring traceability of drug and patient data between actors is a breakthrough in the speed of clinical trials and the efficiency of collaboration, and thus productivity. It also helps to battle many of the problems associated with i.e., counterfeit drugs, which can be seen as one of the biggest threats to the pharmaceutical industry (Uddin, 2021).

4.2.4.3 AI and ML

AI and ML are two very hot topics in the pharmaceutical industry where R&D scientists are working hard to discover new ways to find and engineer new groundbreaking drugs. Today, both AI and ML have been successfully implemented in all the different stages of drug discovery in different ways and they can be used to bypass all different types of shortcomings (Malandraki-Miller & Riley, 2021). AstraZeneca and Novartis appear to be at the forefront of using AI and ML to improve their processes.

For example, according to Chan et al. (2019), the uses for AI include the screening of drug assays, predicting important elements such as physical properties, bioactivity, toxicity, structure, and protein folding, processing of cell images, and planning of chemical synthesis. Things such as structural biology that usually take years to perform can with the use of AI take as little as days or hours. A successful example of this is Takeda which collaborated with Recursion Pharmaceuticals to bring the pre-clinical drug discovery pipeline down to 1,5 years compared to the usual time of roughly a decade (Chan et al., 2019). Also, Malandraki-Miller and Riley (2021) suggest a long list of AI applications in the likes of performing predictive analysis on real-world data to increase the success rate of clinical trials, identifying the best possible patient groups, developing precision medicine, and helping trial sites by making them more efficient.

Similarly, the applications of ML include things such as identifying biomarkers, fast and affordable precision in different medicine methodologies, different types of predictions, possibilities to study drug-to-drug interactions, data contributions in pre-clinical stages, and simpler progression in clinical trials. This is good because roughly 40% of all newly approved drugs in 2018 were personalized, and ML can help improve this field of development further (Malandraki-Miller & Riley, 2021). Other general advantages of ML consist of decreasing human error, making therapies more patient-oriented, facilitating standardized and transparent data control, and assessing and comparing the efficiency of candidates before testing. These are all relatively inexpensive ways that ML can be used to increase productivity, through automation of data processing and analysis (Malandraki-Miller & Riley, 2021).

4.2.4.4 3D-printing

3D printing is a way of manufacturing that can yield great productivity increase for companies in the pharmaceutical industry. One of its uses lies in actual manufacturing, where it can offer additional functionality and flexibility not seen today. For example, as suggested by Zhu et al. (2020), it can be used to create drugs with very complex structures to promote drug absorption, reduce adverse drug reactions, control the release rate, or on-demand to control dosage accuracy, among many things. These claims are also supported by Beg et al. (2020), which states that 3D printing is especially relevant for customized drugs. However, its greatest

productivity use does not lie in actual manufacturing, but rather in situations for drug testing and research. 3D printing is an efficient tool in drug trials since it can be used to to grow organs or organ-on-a-chip, control cell distribution, or simulate extracellular matrices and biomaterials. This drastically reduces the time and cost for trial subjects and can thus help decrease the time to market for new drugs (Zhu et al., 2020).

5. Results and analysis of interviews

This chapter will present and analyze the material collected during the interviews. To give structure to the analysis, the interview material will be sorted by relevant categories identified in the interviews, see section 2.5. The qualitative data collected in the interviews will then be analyzed and compared to the literature study and previous research on the topic. In the following chapter, the interviewees will be presented with both their first name and their surname the first time he or she is mentioned in a subheading. For easier readability, this will recur for every subheading. However, if the interviewee has been mentioned before in a subheading, only the surname will be used. In addition to this, to further strengthen the readability, the company that the interviewee is working for is presented in parentheses after his or her name the first time in each subheading that the interviewee is mentioned. The statements in the following chapter are merely personal and not linked to the company the interviewees work for. Therefore, it is paramount to understand the distinction between the personal opinions of the interviewees and the company they are working for. Would the reader inquire for more information regarding the interviewees, this can be found in Table 1 in chapter 2. As a final comment, the results indicate that the respondents focused on six overarching themes relating to productivity.

5.1 Increased scientific understanding and its impact on drug development

As established in the literature chapter, the industry has in recent years experienced a shift in the types of drugs that are developed; a shift towards oncology and rare diseases facilitated by an improved scientific understanding (recall Figure 9 from section 4.2.1.3). Our findings based on the interviews verify the existing research but also adds nuance in terms of challenges, opportunities, and future perspectives on what types of drugs are developed.

Dag Larsson (LIF) states that: “The industry, including larger companies, has gone from Blockbuster drugs with huge patient populations to more precise treatments with small patient groups”. Elisabeth Björk (AstraZeneca) adds that: “It is very difficult to be productive in the cardiovascular disease area since a lot of that area has already been covered”, highlighting the role of new disease areas for improving productivity. This is further expanded upon by Yilmaz Mahshid (Medivir) stating that:

> “Up until the late 90s, drug development was focused on widespread diseases [e.g., cardiovascular disease and diabetes]. Then, the human genome was sequenced, allowing for increased patient group specificity and the exploration of diseases that had not previously been explored. For example, in oncology, there was a shift from giving everyone chemotherapy to instead developing drugs towards specific proteins,

enzymes, and receptors which was based on an improved understanding of genetic mutations driving cancer."

This quote highlights the perspective that increased scientific understanding has facilitated the shift of the types of drugs developed, thus being central to the productivity shift.

Mahshid further specifies that: "Although the genomic breakthrough came 20 years ago, the long lead times until regulatory approval, means that it is only in the recent decade that approvals for targeted medicine have accelerated". Mahshid's statements suggest the importance of increased scientific understanding regarding precision medicine, and that an understanding of the human genome is fundamental for future innovation in the pharmaceutical industry. This relates well to the data presented in Figure 9 showing an exponential increase in the average number of mechanisms of action of a drug over time, starting in the 90s.

Mahshid also highlights the rise of biological drugs such as antibodies as a result of the sequencing of the genome. The significance of antibodies is further established in the literature study where Pammolli et al. (2020) states that monoclonal antibody-based drugs have shown the largest increase within oncology. Anna Törner (SDS Life Science, SDS Medteq) agrees with Mahshid, and she states that "Biologics will increase because you will be able to address more complex targets".

Jakob Lindberg (Oncopeptides) mentions that there may be further reasons behind the growth of orphan drugs and precision medicine beyond the improved scientific understanding. Lindberg highlights the role of the regulators, for example, the Orphan Drug act of 1983, and financial incentives such as Priority review vouchers, as drivers for the acceleration of drugs for diseases with smaller patient populations such as pediatric and tropical diseases. Christian Sonesson (Egetis Therapeutics) states that the vouchers can be sold for considerable sums since they will extend the time on the market before patent expiry.

Another significant finding is the debate on costs, revenue, and profitability relating to pharmaceutical drugs in general and orphan drugs and precision medicine in particular. According to Anna Törner, a driver behind the accelerating costs for drug development may be related to the increased biological complexity of drugs combined with niched therapies for smaller patient populations. Several interviewees also agree that this may lead to consequences such as higher therapy costs for the patient.

Sven-Olof Lager (AstraZeneca) states that: "Going towards precision medicines will lead to smaller volumes but it will allow for a higher pricing of the drug". Törner has a similar view as Lager, but adds a perspective when she brought up a point: "We will end up in a scenario in the future where we produce pharmaceuticals that we barely can afford". Mahshid adds another perspective to the discussion mentioning that the potential lower revenue, that may result from the price increase of precision medicines not being able to counter the decrease in patient population size, will be countered by lowered marketing costs. Mahshid even goes as far as stating that the decrease in costs will be so great it can improve profitability. Christian Pitulia

(Cellink) adds to the discussion stating that: “If you look at the overall perspective, and healthcare costs in general, the costs may decrease in the future due to better medicines and therapeutic methods, although it may become more expensive in the short term”.

Another relevant finding is how increased scientific understanding has set a temporary break on the ‘better than the Beatles’ problem. Mahshid states that:

> “The specificity of patient populations based on their exact mutation has opened an avenue for approving drugs since it can be argued that there are no preexisting drugs for that specific disease, and thus lowering the bar for approval.”

Björk adds a perspective relating to the future of drug development and how to address competition. She highlights that it is important to understand the future: “What type of disease panorama will exist when we have treatments for the current diseases? If people do not die of cancer, what will they then die of?” This adds an important concluding perspective on the types of drugs that are developed, and it highlights the everchanging landscape of the industry, and that we will never run out of diseases to treat.

Another shift brought up by Lena Sjögren (AstraZeneca) is that the company she works for starts earlier to look for additional possible indications. To maximize the use of each drug candidate is a trade-off between financial incentives and the risk and costs related to extending projects.

All in all, the interviews indicate a shift away from the blockbuster drugs and towards the drugs that address the diseases that kill us today, such as cancer, and rare diseases where there is a large unmet need which can be argued to be a key behind increasing R&D productivity. This shift is linked to changes in cost and revenue structures, and it has diversified the industry. As indicated by the interviews, the industry has left certain productivity issues behind, such as difficulties with finding new treatments in already saturated markets, but new issues such as increased complexity and higher cost for the paying patient arise.

Relating this factor to the factors established in section 4.1 that describe the underlying causes of Eroom’s law, the most prominent effect the increased scientific understanding has had is related to the ‘better than the Beatles’ problem. Allowing for a wider disease spectrum means there can be more diverse drugs that are developed, opening up more avenues for drug development. What can be concluded is that this increased understanding has been a key factor to improving productivity in the past decade with an increased focus on target-specific oncology for example. Though what remains unknown, is for how long this change will hold.

Furthermore, scientific understanding such as genomics can also be considered to counter the ‘basic research – brute force’ bias by giving researchers the ability to better understand the disease drivers on a genetic and molecular level. This allows the researchers to work in a more systematic target-based way with a better understanding of how it may impact the individual beforehand, thus contributing to productivity and better resource allocation.

5.2 Externalization of R&D

A recent, major trend shift observed in the pharmaceutical industry is the upswing of M&A activity at the beginning of the 21st century, as elaborated on in chapter 4. As bringing a drug to market requires 10 to 15 years on average, any approval-related effects of this trend shift coincide chronologically with the observed trend shift in productivity, indicating externalization of R&D as a plausible, partial explanation.

The observed increase in M&A activity is supported by the perceptions of several interviewees and contradicted by none. Furthermore, Jakob Lindberg (Oncopeptides), Anna Törner (SDS Life Science, SDS Medteq), Christian Sonesson (Egetis Therapeutics), and Yilmaz Mahshid (Medivir) all argue that large pharmaceutical companies' interest in acquisitions stems from smaller biotech companies having greater innovative capacities.

Lindberg suggests that innovation is associated with considerable diseconomies of scale:

> "The discovery process of pharmaceutical research is completely dependent on individuals. . . . Passionate and creative individuals capable of drafting clever and correct hypothesis and breaking known patterns constitute the entire key to the innovation process. . . . Then the next problem presents itself: these individuals are generally dissatisfied in large, process-oriented organizations. It is obvious that they are difficult to contain within large organizations, as large organizations are coordination-oriented. And coordination means process, and process means control. It becomes like oil and water."

According to him, small biotech companies are more capable of attracting these crucial creators, as well as providing them with the creative freedom they require to successfully innovate. Thus, Lindberg explains, large companies have addressed their inability to efficiently innovate by increasingly abandoning internal drug discovery in favor of acquiring externally discovered projects. He identifies this adaptation as the driving force for the productivity changes observed, summarizing that "the driving force is innovation's palpable diseconomies of scale; if you put enough people in a room, they stop innovating". Mahshid shares a similar view, expressing that:

> "About 15 years ago, externalization of R&D became popular; i.e., acquiring external expert knowledge is favored over internal discovery. . . . Large companies have a harder time innovating, partially due to having more corporate politics. When speaking to Big Pharma employees, you hear stories about them spending 50% of their time on internal politics and 50% on actual work."

These perceptions align with the findings in section 4.1, relating to pharmaceutical R&D productivity, with existing literature claiming that managerial efforts in larger companies to introduce a higher degree of structure, discipline, and formality to the previously free and open research environment in practice have suffocated creativity and freedom. This, in turn, is

closely related to the 'basic research – brute force' bias in Eroom's law, which partially blames modern management practices for bringing industrialization to pharmaceutical R&D.

Therefore, externalization of R&D does propose a solution to an identified factor behind decreasing R&D productivity, and the M&A trend does indeed appear to be a logical contributor to the observed shift in productivity. Interestingly, Dag Larsson (LIF) further points out that "large companies with all R&D in-house risk missing out on the agility and smartness that exists in small organizations". As increasing externalization coincided with a shift in the types of drugs developed, this indicates that increased agility may have been especially profitable during the past two decades. It is worth noting that this explanation connects the decrease in R&D productivity to the discovery processes in Big Pharma alone, and framing smaller biotech companies as its solution. Lindberg acknowledges this, and argues that "the productivity in small companies has been very high during the past decades".

Furthermore, Lindberg and Sonesson both predict that the externalization of R&D discovery will continue to increase, leading to an R&D environment where small biotech companies specialize in the discovery and early development to then sell or license their results to larger pharmaceutical companies, that in turn specialize on the late-stage development and commercialization. This is in line with the prediction of increased outsourcing of research presented in section 4.2.2 made by Statista in 2016. "Big Pharma is positioning themselves further downstream in the value chain, like purchasing or umbrella organizations and practitioners of open innovation. Thus, economies of scale are easier to leverage within sales than innovation" Sonesson explains. Lindberg shares a similar view, stating that "large companies should slim down their discovery functions and focus only on in-licensing and acquisitions", arguing that continued investment in internal discovery while the lion's share of new molecules is purchased from external actors means paying for the results twice. In addition, Lindberg emphasizes how the externalization trend is the result of the discovery and early phases of drug development exhibiting diseconomies of scale, while the subsequent stages show clear economies of scale, stating that:

> "I believe in development towards innovation systems where the innovation element is distributed over small, academic players and SMEs, while the larger companies act like motherships, purchasing and licensing innovation to conduct late-stage development, commercialization, production, and logistics. This because the early phases have strong diseconomies of scale, while the late clinical development phases and the commercialization phase have very clear economies of scale."

Lindberg goes on to compare the development to that of the automotive industry in the 1960s. He explains that:

> "Before, the automotive industry was monolithic, but then it started placing part of the innovation activities on suppliers and decided to focus on assembly and branding. The same thing has happened in the pharmaceutical industry, which essentially was

> monolithic until the turn of the millennium. . . . Pharmaceutical companies outsource the difficult innovation element and focus on commercializing externally acquired results."

The concept of economies of scale in the later stages of drug development and commercialization is moreover supported by Jan Nilsson (Combigene), who explains that "their presence in a large number of countries and their ability to simultaneously market a product in the entire world, is Big Pharma's big strength".

By contrast, prior research presented in section 4.2.2 instead shows something of a convergence between biotech and pharmaceutical companies. The new, smaller indications pursued, paired with the upswing of CROs, is increasingly allowing smaller biotech companies to commercialize their innovations independently, the existing literature argues.

Additionally, Elizabeth Björk (AstraZeneca) maintains that large companies also hold advantages over their smaller counterparts in early developmental phases. She explains that:

> "Large pharmaceutical companies have the advantage of being active within more and larger research areas. This allows them to identify new applications for pharmaceuticals, while smaller companies may not be able to do so, due to being heavily specialized in their focus. An example from AstraZeneca is a pharmaceutical intended for diabetes patients proving to also have positive kidney effects."

In summary, several interviewees make a connection between increased M&A activity, Big Pharma's externalization of innovation, and more efficient R&D. Literature and interviewees alike seem to identify diseconomies of scale in the early phases. Meanwhile, regardless of the CROs eventual impact on clinical trials, the existence of economies of scale in certain later development phases (e.g., marketing and production), as argued by interviewees, seems likely. Thus, increasing M&A activity appears to be an additional contributor to the increased productivity observed. In part, this contribution is achieved through addressing two established causes of the previous decrease in productivity: organizational problems (as per section 4.1.2) and the 'throw money at it' tendency (as per section 4.1.1). The results indicate that small organizations can sustain lower degrees of coordination, which in turn strengthens an innovative environment and counteracts the organizational problems factor. Additionally, it is deemed probable that these small organizations, through less required coordination and a more minimalistic corporate structure, will spend less capital on superfluous human resources and are less likely to believe that the organizations' professional success is proportionate to the size of its budget. Thereby, the industry's wide trend of placing early R&D phases on these organizations also addresses the 'throw money at it' tendency.

5.3 The interaction with regulatory agencies

Our interviews showed that there are examples of both regulatory reliefs and regulatory aggravations for pharmaceutical companies. In addition, the consensus seems to be reached that the regulatory agencies have enabled better dynamics and more adaptive processes. Also, the ability to communicate and meet with regulatory agencies has been highlighted as an important factor to increase the productivity in pharma companies.

Additionally, it can be said that there are many regulations in the pharmaceutical industry due to safety concerns and quality assurance. These regulations have evolved over several years as new technology has emerged and new drugs have been developed. Jakob Lindberg (Oncopeptides) states that the regulatory agencies act more flexibly now than 40 years ago and have not developed to become more rigorous. Instead, they have developed to become smarter. For example, Lindberg states the following: "To a greater extent, the regulatory agencies act as a partner to the drug developers with the main aim of helping patients. They no longer have the default setting to say no." Dag Larsson (LIF) is of a similar opinion and asserts that the thresholds are not lower for new drugs. In lieu, he states that: "Today, if you have the 'right' drug, it is less challenging to develop a new drug than before. Despite this, it is not easier to receive approval for a 'bad' drug."

Another important perspective relating to productivity is that of cost efficiency, which is illuminated by Jan Nilsson (Combigene). He mentions that new drugs must not only show higher efficacy than previous drugs, but the applicant must also show that the drug candidate is cost-efficient. He highlights how the cost requirement has increased over time, which could be a contributing factor to decreasing the cost to develop a new drug, and thus improve productivity since the agencies are more selective in regards to the cost aspect.

On the other hand, Nilsson also casts light upon examples of regulatory reliefs. One example of a regulatory relief is the adaptive clinical trial designs that are described more thoroughly in sections 4.2 and 5.4. This example of a regulatory relief could be a way to help align the goal of the regulatory agencies with the goal of the industry; to bring drugs to the market in a financially viable way, which Anna Törner (SDS Life Science, SDS Medteq) states is a significant aspect as costs increase exponentially through the clinical trials. The fact that costs increase exponentially through the clinical trials is in line with the fact that the attrition rates of late-stage trials have the largest effect on R&D costs, as stated in section 4.2.3.

Even though there are slightly different opinions regarding the development of the regulations over time, the consensus seems to be reached that the regulatory agencies have enabled better dynamics and more flexible processes. Not only is this change beneficial for pharmaceutical companies in terms of productivity, but, in the end, also for the patients. Johannes Hulthe (Antaros Medical) summarizes this well when discussing the development of the regulations:

> "Seen to the short term, I cannot speculate whether the regulations have become stricter or not. However, it is certain that during the last 70 years there has been an enormous change in both regulations and what is expected regulatory concerning ethics and the process of approval in clinical trials. All this entails more time and resources, but the advantage is of course that there are much more safe processes where the patients' integrity and safety are assured."

Moreover, the possibility to communicate and meet with regulatory agencies has been highlighted by Nilsson as an important factor to increase the productivity in pharma companies. He expresses that dialogue with regulatory agencies is important for guidance and to understand the potential of the drug candidate. Additionally, he says that it is just as important to understand what not to invest in as the importance of understanding what to invest in. Nilsson expresses that:

> "We can meet the agencies. We can have meetings with them, we can get support and their guidance during the start of the journey of developing a drug and all the way forward. So, it is something very positive and it increases productivity because you get early indications of whether this can fly or not."

Törner and Larsson are of similar opinions. Törner states that there is a lot of help that can be received from regulatory agencies if there is a medical need for it. For example, Larsson highlights the role of scientific consultation, which means that actors in the pharmaceutical industry receive consultation on how to set up their development program and invest their money to drastically increase the probability of success. However, according to Törner, the possibility to have a dialogue with regulatory agencies regarding the development of drug candidates is not something new.

Therefore, how the possibility to have a dialogue with regulatory agencies is related to the increase in productivity seen from 2010 and forward is unclear. Instead, a possible reason for the productivity increase seen from 2010 could be that this dialogue has borne more fruit. Additionally, Lena Sjögren (AstraZeneca) and Sven-Olof Lager (AstraZeneca) provide an interesting perspective regarding the cooperation with the regulatory agencies:

> "In the already developed areas that the agencies are aware of, there are usually no problems. Bringing new drugs forward can go quickly, but when the drugs are a little more innovative, I see a clear change of attitude from regulatory agencies. However, I do not say that it is wrong. An area still up for discussion though, lies in how the regulatory agencies deal with new technologies and new models, e.g., genomics and mRNA. They are not on the track yet when dealing with this, which means it can be very expensive and take a long time to get that type of new drug approved."

This quote highlights that it is important that the regulatory agencies are up to date and have an extensive understanding of up-and-coming topics to promote productivity and effective discussions.

Furthermore, Törner states that regulatory requirements and the need for data increase exponentially when moving from one phase to another within the clinical trials, to ensure safety and efficacy. As a result of this, Törner discusses that smaller pharma companies with much fewer resources have considerably larger difficulties taking a drug all the way to the market.

To cope with the rigorous requirements of the clinical trials, many smaller pharma companies see it more financially viable to sell or license out their drug candidates in the preclinical stage or in an early phase of the clinical trials than to take the drug to the market by themselves. According to Nilsson, the price tag for the different drug candidates is not linear to the phase they are in. Instead, he says that Big Pharma companies pay a relatively small figure for the drugs in the preclinical stage or the early phases but a very hefty figure in the later phases of the clinical trials. Therefore, it can be argued that the incentives for smaller pharma companies to sell or license out in a later stage of the development of a drug are greater. However, the smaller pharmaceutical companies may be counteracted to sell off in a later stage by the scrupulous regulations that often hinder them to develop their drug candidates by themselves in the clinical trials.

When selling or licensing out, the risk of the drug not being approved is either transferred to the buying company or shared with it. Since the buying company often is a Big Pharma, i.e., a pharma company with enormous resources and standardized processes, it has a greater chance of taking the drug candidate all the way to the market. This is something that several of the interviewees have brought up. When discussing what is necessary to successfully develop a drug and taking it to the market, Hulthe highlights the importance of experience in the organization by stating: “Reaching success is an art, and is difficult to learn by reading books. In some way it is that you have been on the journey several times before. The key is experience”. Törner shares a similar opinion and states that:

> “The requirements are generally the same for Big Pharma and biotech companies. However, biotech companies have a disadvantage. Due to the expertise and knowledge in Big Pharma companies, they have the resources and knowledge to do it right from the beginning. On the other hand, biotech companies tend to make more mistakes.”

From Figure 12 in the literature study, it can be seen that the attrition rates for Big Pharma companies and biotech companies are very similar, which seem to indicate a discrepancy between the interviewees’ perception and the statistics of which of the actors have a better chance at taking a drug to the market.

All in all, it can be said that there are slightly varying opinions regarding the development of the regulations, and a consensus seems to be reached that the regulatory agencies have enabled better dynamics and more adaptive processes. In addition, there are examples of regulatory

reliefs such as adaptive clinical trial designs and regulatory aggravations such as an increased focus on cost efficiency for new drugs. Also, smaller pharma companies with fewer resources have more difficulties in terms of clinical success and marketing with taking a drug all the way to the market. Consequently, biotech companies can see it more financially viable to sell or license out their drug candidates. Big Pharma companies, with their enormous resources and standardized process, have a greater chance of taking the drug candidate all the way to the market. Moreover, the ability to communicate and meet with regulatory agencies has been highlighted as an important factor to increase the productivity in pharma companies. What can be said though, is that regulatory agencies must be up to date and have an extensive understanding of up-and-coming topics to promote productivity and effective discussions with actors in the industry.

Ultimately, communication among actors and regulatory agencies can be seen as a prerequisite to foster higher productivity in the pharmaceutical industry, thus indirectly impacting productivity. Early communication with regulatory agencies can indicate whether a drug candidate has the potential of being successful or not, and by implementing this there are possibilities for productivity increases in pharmaceutical companies. For especially biotech companies, with fewer resources and generally less experience among the employees, this communication with the agencies is key. In addition, early communication can be a contributing factor counteracting the ‘basic research-brute force’ bias claiming that there is a tendency to overestimate the ability of advances in basic research to show a molecule safe and effective in clinical trials. By communicating early there are possibilities for more realistic expectations to be set on the outcome of the clinical trials. However, the communication with regulatory agencies is not something new and the result can therefore not reveal a direct connection between the communication and productivity increase seen from 2010 and forward. Nevertheless, a possible explanation for the increase in productivity could be that communication has borne more fruit.

Despite not dealing with the critique against the regulatory agencies, the following quote from Nilsson summarizes the current relationship between pharma companies and regulatory agencies well: "It's not us or them anymore; we have a common interest in developing good medicines for patients”.

5.4 Changes in clinical trials: a shift from cautious to adaptive

The main reason for clinical trials is to ensure and prove the efficacy and safety of a drug. Due to the change in drugs developed, from mainly blockbuster drugs to more rare and specific drugs, new ways of conducting clinical trials have emerged.

As mentioned in section 5.1, the large number of drugs already targeting big indications, such as cardiovascular diseases, makes it difficult to find innovative drugs adding substantial value within these indications by posing something of a ‘low-hanging fruit’ problem. Anna Törner

(SDS Life Science, SDS Medteq) states: “Since we are looking for smaller incremental improvements, larger and larger clinical programs will be needed for approval”. She further explains: “Before, a study with 400 patients could be sufficient within cardiovascular disease trials. . . . nowadays you need about 4000 to 8000 patients to get through the trials of a drug with a marginal increase of efficiency”. Since the efficiency is often marginally increased, huge clinical programs, compared to before, have to be introduced to statically prove the increase of efficiency. These trials often contain thousands of patients, which increases the cost of the trial and increases the overall cost of getting the drug to the market. This size and cost development could be a fundamental reason for the productivity decrease, which has been countered by the industry with adaptive designs and an increased focus on innovative drugs, which has also been established in the literature study where Pammolli et al. (2020) suggested an increased focus on innovative drugs.

Törner points out that the regulatory agencies have made it easier for companies targeting rare diseases, where the patient population is small. An issue identified with having smaller patient populations that multiple interviewees agree with is that it can be more difficult to find patients for trials. One example is Niclas Stridsberg (TLV) who relates the rapid development of Covid-19 vaccines to the abundance of patients for trials, showcasing that the opposite may be detrimental to R&D productivity. Although, Anna Törner states that there already exist centralized patient registries for some diseases, which enables easier and cheaper coordination of clinical trials. This could be key to enabling productive R&D. It also aligns with Figure 8 in section 4.2.1.2 of the literature study, illustrating how the POS has increased for rare diseases.

From the interviews, it can be concluded that it is necessary to find more effective ways in how the clinical trials can be done. Sven-Olof Lager (AstraZeneca) mentions that finding patients for clinical trials can be hard, especially during Covid-19. Lager explains that companies have to find ways to work with universities and other external organizations with databases, to easier gather the data required. Lena Sjögren (AstraZeneca) backs this claim up by saying that:

> “We have to work continuously with finding more effective ways to conduct the studies, I think that one thing that will be used more and more, is the use of secondary data, meaning data that we can collect from already existing databases.”

Törner states that the agencies have become more positive towards adaptive clinical designs, instead of the traditional designs. However, the adaptive clinical designs are mostly used for innovative drugs and are rarely used to find a small increase of efficiency in an already existing drug. This has allowed companies to get innovative drugs out on the market faster, to help patients when there are no other treatments available while maintaining statistical significance.

One example of how the use of databases can improve productivity by lowering the cost is a project that Elisabeth Björk (AstraZeneca) mentions. Björk explained that they used patient records and journals from hospitals, instead of conducting a whole new study to gather the data. This project had its cost reduced by 60 %. Another important aspect of this project was

that it was only conducted in two countries, Sweden and England, and according to Björk, the number of countries you conduct the studies in has a high effect on how expensive the study will be.

A significant problem in clinical trials according to Törner, is that for some indications it is very difficult to show efficacy and safety reliably. She brings up the example of finding drugs to treat traumatic brain injury, for instance for patients after motorcycle accidents. Törner states how this has long been a very difficult indication due to the large variation in the size of the trauma from patient to patient combined with poor instruments to evaluate baseline status and outcome. She continues describing the difficulties in gathering data that is related to the diagnostic method used. The Glasgow Coma scale measures the injury on an ordinal scale, and Törner emphasizes that it can still be difficult to know "what is a 4 on the scale?", and she says that small improvements make it difficult to ascertain with certainty. When only this type of scale exists, it results in insufficient data and it is therefore difficult to measure any minor improvements that could come as a result of the drug, thus making it difficult to prove efficacy with a high degree of significance. This shows the importance of developing proper diagnostic tools in regards to facilitating productivity, especially when the industry wants to show smaller but still significant improvements.

Furthermore, to overcome the problem of long timelines in the trial, and to increase productivity, Törner suggests that new ways of measuring and prove efficiency have to be used. She explained how the pharmaceutical industry overcame a problem addressing kidney failure and transplantation. Törner states:

> "Imagine a kidney disease, and you have a treatment that will keep you from having a kidney transplant in 20 years, however, companies do not want to make studies that last for 20 years. Instead of having this long study, a surrogate endpoint could be used to shorten the time."

Törner explains that "if a surrogate endpoint is used to measure the effectiveness of treatments that predicts the outcome for the clinically relevant endpoint, the agencies can approve this method".

As can be seen, many things have happened relating to methods to prove the safety and efficacy of a drug that affects productivity both in positive and negative ways. For instance, many of the big indications have already been explored, which as a consequence means that clinical trials must be larger to prove minor improvements. At the same time, more innovative drugs have emerged during the past decade, and as a result, the regulatory agencies have accepted new methods for proving safety and efficacy such as adaptive designs and surrogate endpoints. In other words, the regulatory agencies have become more flexible with regulations, depending on what kind of drug is being developed. Therefore, 'the cautious regulator' problem has to some degree been overruled by the adaptive clinical designs, where there are regulatory reliefs instead of regulatory aggravations.

Furthermore, in the literature study, section 4.2.3.1, it is brought up that the adaptive clinical designs can reduce cost in the clinical trials, hence improving the productivity in R&D. But it is also stated that complex analysis and generating good data, is necessary to complete an adaptive clinical design, and if this is delayed, a possible productivity decrease could occur.

Overall, the adaptive clinical designs enable certain drugs to reach the market faster and for example decreases some of the difficulties of clinical trials that can be related to patient sample size, such as trial cost, thus directly promoting productivity and facilitating research in newer research areas by decreasing trial costs which an important aspect of the productivity measure. There has been a shift within the regulatory agencies, where they take into consideration the necessity of the new drug, e.g., if there are any treatments for that indication or not, and whether they should allow for adaptive clinical trial designs. The shift within regulatory agencies can be described as a change from a 'cautious regulator' to an 'adaptive regulator' fostering productivity.

5.5 The role of digital technology to improve productivity

Overall, the interviewees see technology as a benefactor of increased productivity during the last decades and believe that it will only continue to become an even more important factor in the future. Not a single interviewee disputed this idea. Interviewee Lena Sjögren (AstraZeneca) also stated that the current corona pandemic has advanced the use of digital technology further since they have been forced to implement it for themselves and their patients.

According to our findings, the biggest current use of digital technology lies in digitalizing clinical studies by accelerating and simplifying different kinds of processes. Sjögren said:

> "Right now, we are currently starting a study in Europe with 15 000 patients that will be run completely digitally via an app except from two physical injections. A year ago, we would never have been able to start a study like this as quickly."

Initiatives like these lead to great improvements in efficiency and are mainly due to the advancement of their use of digital technology. Another explicit example of how this can be done was formulated as designing clinical studies without doctors involved or automatic integration of AI to look at texts and codes and in turn translate it into certain diseases. These are actual uses that are currently in action and that have been confirmed to substantially increase productivity according to the respective interviewees.

The findings from the interviews also indicate that a lot of work is being put into developing different types of digital platforms. How these contribute to productivity differs depending on the type of platform, but one example that was brought forth includes coming closer to the customer and collecting data from the patient straight into their databases. Johannes Hulthe (Antaros Medical) mentioned working with digital platforms that utilize AI to e.g., improve diagnostics by finding patterns and deviations that otherwise would not be found.

When interviewed about regulation and technology, Christan Pitulia (Cellink) and Sjögren stated that they still need to have more discussions with the regulatory agencies when it comes to questions like patient security and data integrity, et cetera. In some ways, regulations prohibit the optimal use of technology for productivity. Jan Nilsson (Combigene(also noted that technology implementation used to go faster, but today it is harder with more strict regulations.

Other interesting aspects that were brought forth were the long time it takes from the discovery of new technology to the actual use of it and the importance of great user experience to accelerate this process. Pitulia argued that while different technologies have been proven to be able to increase productivity, they can be very hard to use. Great technology is thus not enough by itself to increase productivity, but the doctors and biologists – whom of which are not tech-people – need to be able to use it effectively. With great user experience, a shorter or easier threshold to begin using the technology and its applications can be created.

However, it has not become clear that digital technology eases any of the four main causes of Eroom's law previously established. While it is likely that digital technology has been contributing to increased productivity during the past decades in different ways, the interviews have not provided enough scientific evidence to conclude it as an underlying factor for the turnaround. Though, digital technologies have the potential to directly influence productivity by both decreasing research costs by using patient journals and increasing output by using intelligent aids to find suitable targets. The impact of technology on R&D productivity is further discussed in chapter 6.

5.6 Managerial efforts to promote productivity

As established in the literature section, there has been a decrease in the number of initiated early-stage clinical trials, which implies overall lower costs for clinical trials (recall Figure 15). While this could indicate that companies are doing a decreasing amount of innovation, our interviews provide a different explanation: companies are becoming more selective early on to reduce costs and promote productivity.

Christian Sonesson (Egetis Therapeutics) states that companies have moved away from the thought of industrialization of drug discovery with the simple target of pushing a certain number into clinical trials, hoping that at least one will make it through. This is similar to the 'basic research – brute force' bias as described in section 4.1, which could drive large costs for clinical trials. Similarly, Dag Larsson (LIF) brings up the concept of High Throughput Screening (HTS) which is the systematic testing of every molecule, and he states that it has been abandoned in favor of a better selection principle based on an improved biomolecular understanding. On the other hand, Jakob Lindberg (Oncopeptides) states that the industry to some extent is falling back into old habits of automation of drug discovery because of new technologies such as AI and ML. Thinking that the computer will give all the answers if you just push the start button.

Though, the concept of improved candidate selection is further verified by Lena Sjögren (AstraZeneca) who states that: “We try to kill our projects sooner . . . in phase 3 especially we want to have 80-90 % probability to succeed. We are immensely better now compared to 10 years ago.” Elisabeth Björk (AstraZeneca) adds that at her company they have successfully implemented the 5R framework as discussed in section 4.2, as a way to ensure the right products are developed, enhancing productivity. Johannes Hulthe (Antaros Medical) adds a perspective when he states that “The companies have a larger toolbox to early on evaluate safety and efficacy of drug projects”. These examples highlight how new technology and managerial efforts can be used to promote productivity by enabling earlier scrutinization of projects.

Sven-Olof Lager (AstraZeneca) also adds the commercial perspective to the discussion, stating that they look into whether the project will give the return on the investment required to give them their desired gross margin if it succeeds. He mentions the significance of the integration of different company functions such as early and late development and the commercial function to a productive development of drugs.

This suggests that it is also important to bear in mind the commercial perspective when evaluating a drug candidate, especially when agencies are reaching their maximum willingness to pay. Anna Törner (SDS Life Science, SDS Medteq) stated: “When I was young, the agencies paid for every drug, nowadays it may be so that getting the agencies to pay for the drug is the most difficult hurdle to overcome.”

Another fundamental finding relating to fostering innovation, in addition to having good methods for selecting the right drug projects, is the role of talented individuals and facilitating their creativity.

Larsson states that previously the thought was that “The larger the research organization, the better the productivity”, whereas the understanding based off of the interviews is that as Lindberg states, “there are clear diseconomies of scale to innovation” and Jan Nilsson (Combigene) brings up that “there is an inverse relationship between innovation and the size of an organization because many people want to have their say, internal processes and control functions”.

On the other hand, Lena Sjögren highlights the role of a governance structure where people from the commercial organization assess the early-stage projects, to complement the creative researcher who may rather focus on the scientific discovery rather than how to use it in medicine. She also highlighted the role of attracting the most talented individuals when she said that AstraZeneca moved their R&D site in England from Alderley Park to Cambridge to get access to the best researchers and cutting-edge science.

The role of small and large companies in regards to innovation is discussed in section 5.2, but what remains clear from the interviews is that no matter the size of the company, it is significant to not crowd the researchers with bureaucracy, and to attract talented individuals to maintain

research productivity. While at the same time maintaining the commercial perspective and scrutinizing projects in time so that they do not waste unnecessary money.

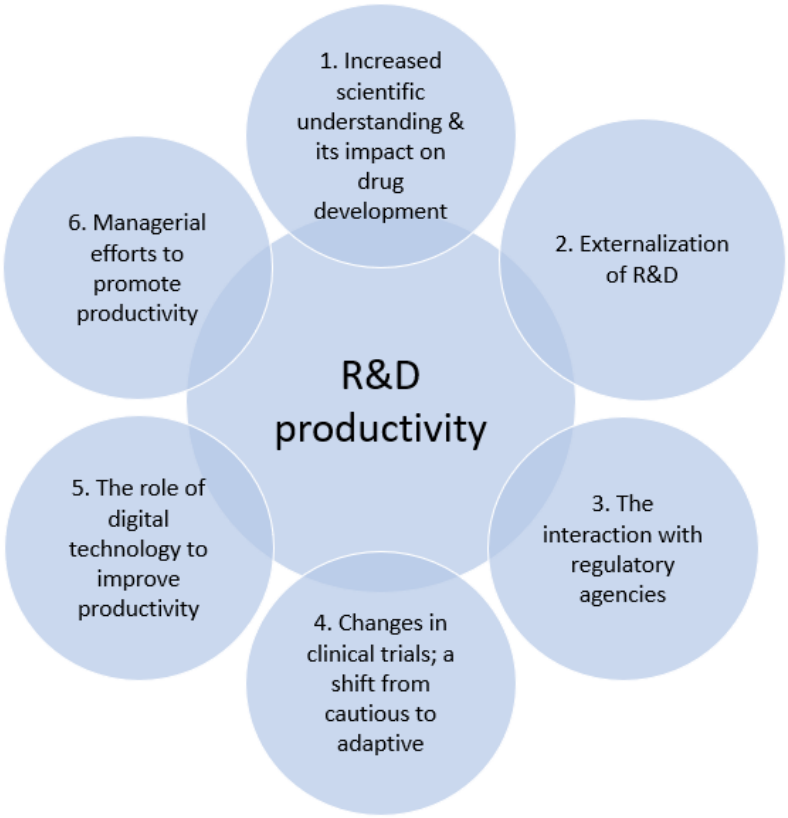
All in all, the managerial efforts, seen in both the literature study and in the interviews, can be a further explanation of the recent improvements in R&D productivity. Especially the fact that companies are moving away from trying to industrialize the discovery process of new drugs to instead use the improved understanding of biological molecules to scrutinize projects earlier and prioritize the projects. By doing so, it can be argued that the 'basic research-brute force' bias has been addressed, and with this improve productivity directly by lowering research costs. However, Lindberg says that there are tendencies in the industry, that the advancement of AI may lead to falling back into old habits of trying to automate the discovery process. Furthermore, to be productive when innovating, the companies have understood that their organization has to have a climate that fosters creativity and innovation, and not just to throw money and resources into the organization. This understanding can be seen as a factor contributing to overcoming the 'throw money at it' tendency.

6. Discussion

The problem discussion highlighted the need to map out the factors behind the observed turnaround in R&D productivity since 2010. Without a fundamental understanding of the underlying factors behind the productivity increase, it is more difficult for the industry to develop strategies to maintain the positive effects and thus have productive and financially sustainable R&D. The results reveal six over-arching factors that possibly can be used to explain the turnaround, as illustrated in Figure 17. Pammolli et al. (2020) explicitly state that it is important to investigate which factors are transient and which are structural, i.e., more permanent. If the factors are not properly explored, there is a risk that productivity falls back into old trends which would further hinder innovation. Further discussion about Sustainability and Ethics related to the research questions can be found in Appendix C.

Figure 17

An illustration of the overarching factors relating to R&D productivity in the pharmaceutical industry.



6.1 Clarification of external and internal factors influencing productivity

The six over-arching factors found in the interviews all have different characteristics in terms of it is internal or external to a company. A majority of the factors are external to the individual company, for example, regulation and the scientific basis upon which today's research relies. Only one factor is explicitly internal; hence it could be argued that the productivity turnaround that has been observed is to a large extent dependent on the common efforts of the industry in terms of shaping the external factors. However, the role of the individual company cannot be forgotten, but it must still adapt to external factors. This highlights the interconnectedness of the industry emphasizing how it must work together to promote productivity.

The role of managerial efforts in section 5.6 stands out as the main internal factor discovered in this study. One example is the 5R framework highlighted in both the literature study and in the interview results. The internal factors can to a large extent be implemented by an individual company to boost their productivity and create a competitive advantage. Similarly, the aspect of facilitating innovation might also be adapted internally by, for example, removing the coordination aspect and bureaucracy with diseconomies of scale, and thus promote a more productive environment.

The external factors on the other hand are shaped by the industry as a whole. Interestingly, the rest of the factors, apart from 5.6, explored in this study are external to a larger extent. The role of increased scientific understanding, the role of the regulators in terms of both new types of clinical trials and communication, new digital technologies, and the externalization of R&D all lay the foundation for today's pharmaceutical industry and all impact the productivity of the industry as a whole. Scientific discoveries such as genomics, mRNA technology, and advances in digital technology such as AI, as mentioned in section 5.1 and 5.5 respectively, are implementable by every actor, even though the productivity that can be gained from them is determined by how well the individual companies adapt to the newly available resources and technologies. Furthermore, regulations are external factors that apply to the entire industry, as well as the new types of clinical trials as established in section 5.4. The way the regulators contribute to productivity in terms of incentives, communication, and adaptations is equal to all industry actors. Because the external factors apply to all actors in the industry, it is difficult for an individual actor, such as a biotech company, to influence them on their own.

Having an understanding of what the internal versus external factors are is significant to future research in terms of understanding how to prevent the factors from returning to their "unproductive" state. It is important to know who must take the action to promote the longevity of the factors.

Also, as mentioned in section 5.5, new digital technologies cannot be linked to contend any of the four main causes of Eroom's law based on consisting evidence. However, it can be argued that new technologies could have influenced almost all of the proposed factors. For example,

digital technologies may have facilitated the development of adaptive clinical designs discussed in section 5.4 and 4.2.3.1, where each clinical trial in some way is unique and demands a great amount of information exchange. The same reasoning applies to the role of regulators as advancements in new digital technologies over the past decades have enhanced communication between regulatory agencies and other industry actors. Furthermore, although some of the proposed factors seem to have eased the 'basic research-brute force' bias as mentioned previously, the industry might be on its way to enter a new nuance of the biased mindset – namely an overbelief in the potential of technology and its ability to solve problems in the industry. We choose to call this the 'technology brute-force' bias and fear that it might join the four main causes of Eroom's Law as a new law attribute in the future.

6.2 The longevity of the productivity increase

As highlighted in section 1.2 and the introduction to this chapter alike, understanding the drivers behind the increase in productivity is an important step towards determining their durability, and in turn, determining the longevity of the break observed in Eroom's law.

The first factor identified to have increased productivity is the emergence of a new spectrum of indications following the mapping of the human genome, as per section 5.1. Whether this factor proves to be structural or transient is entirely dependent on the pace of new medical discoveries driving the field of pathology. The pace has admittedly been high since the beginning of the 21st century, but the limited advancements that preceded the sequencing of the human genome still indicate that it perhaps should be considered a transient, albeit resilient, factor nonetheless. Additionally, the reasoning by Björk and Törner regarding increasingly targeted pharmaceuticals resulting in drastically increasing drug prices through limited patient populations and more complicated technologies makes affordability and willingness to pay an increasing industry concern. This strengthens the transient nature of this factor since it indicates that increasingly specialized medicine might already have reached a point of diminishing returns.

The second factor identified to have increased productivity is the increased specialization through externalization of R&D, as per section 5.2. This factor is deemed likely to be structural, as organizational improvements can hardly be expended. However, large organizations can only slim down their in-house R&D functions once, and consequently, it is also deemed unlikely that this factor will continue to yield adaptative productivity increases over time. Consequently, it should be viewed as a lasting contribution consisting of a one-time productivity boost.

The third factor identified to have increased productivity is the flexible regulation and additional incentive structures which have made new therapeutic panoramas available for research and development, as per section 5.4. Here, the structural or transient nature of the effect is more difficult to determine and closely interlinked with the rate of the continued

growth of the disease panorama. The legislative and regulatory changes are of course transient until changed, but the temporary reliefs in 'better than the Beatles' problem following availability of new indications of research will be expended for any single indication as more and more projects addressing that indication is conducted. Consequently, the longevity of the productivity increase is dependent on continuous advancements in research to create a steady stream of orphan disease et cetera.

The fourth factor identified to have increased productivity is managerial efforts to minimize 'basic research – brute force' bias and efficiently critically evaluate and abandon unfavorable projects early on, as per section 5.6. Similar to the case of externalization of R&D, once implemented, these managerial advancements cannot be expended and thus constitute a structural contribution. By contrast to the externalization of R&D, it is plausible that these new management philosophies can be further developed, increasing the magnitude of the effect over time.

In summary, several of the factors identified have structural characteristics. This indicates that the observed trend shift in productivity indeed could constitute a lasting breakage of Eroom's law. Furthermore, this is emphasized by the fact that several of the factors have relieving effects on the factors driving Eroom's law and the prior decrease in productivity. In turn, that would contrast the conclusion by Ringel et al. (2020), who believes that the underlying forces behind the prior decline "will again take hold once the effects of recent improvements in understanding disease biology and decision-making wane" (p.834).

6.3 A critical reflection on the results

The interviews conducted have, in accordance with research question 2 (RQ2), focused on Swedish actors' perspective on pharmaceutical R&D. A key question when interpreting the results is therefore the degree to which the findings in this study have bearing outside the Swedish pharmaceutical industry. While this national focus constitutes a limitation to the study, the interviews conducted has made it evident that the pharmaceutical industry is highly globalized and that Swedish actors are by no means acting in a vacuum. Instead, many of our interviewees were part of international collaborations and indeed focused on global markets during R&D endeavors. Additionally, all the factors found to be underlying the productivity shift are international by nature and highly aligned with the international research studied (note especially that "regulatory agencies" refers primarily to FDA and EMA as the most influential agencies and that Sweden does not have a national equivalent). Consequently, it is postulated that the external and internal factors presented in results are to a large extent generalizable to the global industry.

Moreover, this study has defined R&D productivity as the number of approved drugs per billion US dollars spent on R&D, following the convention of notable articles within the field. However, other definitions are plausible, and regardless of which one is chosen, it will likely

influence the results. For example, one blockbuster drug may create more value, revenue, and profits than ten drugs targeting small, niche populations of patients and therefore warrant higher R&D spending. However, this aspect is not included in the definition used in this study, which therefore could be accused of favoring quantity of approved drugs over quality. Considering that the results include such a shift towards smaller, more targeted drugs, which potentially could boost the current productivity measure more than the financial results, a critical discussion is warranted. However, alternative productivity measures are not without their flaws and capture different aspects of productivity along with generating different results.

For instance, if considering the productivity measure 'number of patients per billion of US dollars spent', the productivity would instead be very low due to the small population of patients. Therefore, this productivity measure can be considered inherently flawed. For instance, personalized drugs have a smaller patient population, but a lower sales quantity can be compensated by a higher sales price to achieve the same revenue. Thus, the productivity measure would not take into account markets with, for instance, high profitability but instead merely indicate a productivity increase if the number of patients treated increases - independent of the severity of the disease treated. Consequently, that productivity measure would only constitute a social value without accounting for the change of quality of life for the patients, which could be argued is the actual social value. Hence, this productivity measure has not been used since it can be argued to be arbitrary.

Another possible productivity measure could be concerning the financials, for instance, 'ROI of the approved drug per billion of US dollar spent. However, this can be refuted since connecting revenues to certain drugs would require extensive data analyses and also make the productivity measure unnecessarily complex.

The reason for the use of the number of approved drugs per billion of US dollars spent in this study is first and foremost because of its simplicity. When analyzing the underlying factors to the increase in productivity it is convenient to use a simple measure due to the complexity in the analysis, and for the analysis to be comprehensible a simple measurement is advisable. In addition, the same productivity measure has been used in previous studies allowing for easier comparison between this study and other studies. As a final comment on the definition of productivity measure, as the rise of personalized drugs continues, the need for an alternative productivity measure might become increasingly urgent. However, what that productivity measure could be, is left to ponder.

Following the results presented in chapter 5, one distinct factor identified as driving the increase of R&D productivity was the increased specialization of the pharmaceutical sectors through Big Pharma's increasing externalization of early-stage innovation. Through reallocating investment capital (i.e., moving it from large organizations' research departments that are poorly organized for the discovery process), actors within the industry identified this as an important driver for increased productivity. Interestingly, none of the reviewed literature relating to the trend shift in productivity mentioned this as a potential partial explanation. This

indicates differing perceptions between industry actors and academia regarding what affects and drives R&D productivity and constitutes an addition to existing research.

Notably, however, the perceptions on the importance of externalization of R&D did also differ among interviewees. Namely, those employed at large companies neither linked the productivity increase to externalization of R&D nor viewed Big Pharma's exit from the discovery phases as future development. Meanwhile, the interviewees active at small biotech companies either stated that smaller organizations had the greater innovative ability or considered themselves incapable of making a personal judgment but cited it as a widespread industry perception. This implies lacking objectivity from interviewees on the matter, with employees of small companies being proponents of small companies' abilities while employees of larger companies maintain that larger companies are just as innovative. However, when looking at independent interviewees and statistics, Stridsberg and Törner supported the perception of small companies being more innovative and the drastic increase in M&A activity over the past 20 years (as described in section 4.2.2) indicates that early, innovative value is increasingly generated outside of large organizations. Additionally, existing literature about the decline in pharmaceutical R&D, reviewed in section 4.1.2, describes the existence of organizational obstacles for innovation at large pharmaceutical companies and believes them to constitute a partial explanation for the development. Consequently, the interpretation that increased externalization of R&D is a partial explanation to the productivity, along with the perceptions of diseconomies of scale in early discovery phases and economies of scale for later phases and associated organizational theories, are deemed to be credible and correct.

Additionally, the contradictions and the independent perceptions seen regarding the biotech companies' and Big Pharma companies' impact on innovation of new drugs could be interpreted as follows. A conclusion could be that there is an overestimation of their respective abilities to innovate. Thus, it remains unclear whether biotech companies overestimate their ability to innovate, however the possible conclusion that Big Pharma companies are overestimating their ability to innovate new drugs is strengthened. If this is the case, serious consequences regarding future productivity for Big Pharma companies could await. A lack in the understanding of their own ability to innovate could result in an inefficient allocation of capital instead of more productive external alternatives due to a continued investment in inefficient and in-house discovery functions not rendering desirable results. In addition, the risk of paying double, that is to say, both an ineffective internal R&D as well as an efficient external R&D is apparent. However, a perspective of this is the increased degree of M&A that has been observed, indicating that Big Pharma companies somewhat agree upon the diseconomies of scale in innovation and as a consequence instead acquire innovations from biotech companies. Furthermore, it can be argued that if the internal R&D of a certain Big Pharma company is not reduced at the same rate as the externalization of R&D increases for other Big Pharma companies, the future productivity of the certain Big Pharma company could be hampered entailing competitive disadvantages. Similarly, it can be argued that an increased externalization of R&D could increase the productivity of Big Pharma. This reasoning is in

agreement with Lindberg's view, stating that "large companies should slim down their discovery functions and focus only on in-licensing and acquisitions" because the early phases have strong diseconomies of scale, while the late clinical development phases and the commercialization phase have very clear economies of scale.

7. Conclusion

The purpose of this study has been to explore the factors underlying the turnaround in R&D productivity in the pharmaceutical industry for the past decade. To achieve this, the study has been designed in two parts: as a literature study of previous research, and as an interview study with Swedish experts within the industry.

The literature study reveals that the most important factors determining R&D productivity are dependent on what type of drugs are developed (4.2.1), the role of different industry actors (4.2.2), the method used for drug discovery and clinical trial design (4.2.3), and the use of technology (4.2.4).

The interview study indicates that four distinct factors are driving the increase in R&D productivity. Firstly, greater scientific understanding provides a foundation to increase the drug panorama and possibilities, and at the same time enabling more target-based research (5.1). Secondly, increased specialization of the pharmaceutical sectors is made possible through Big Pharma's increasing externalization of early-stage innovation (5.2). Thirdly, the regulatory agencies create incentives and more flexible regulations to facilitate productivity in areas where research or clinical trial design previously has been difficult (5.4). Fourthly, efficient managerial efforts scrutinize projects early with minimum resource waste and thus decrease attrition rates (5.6).

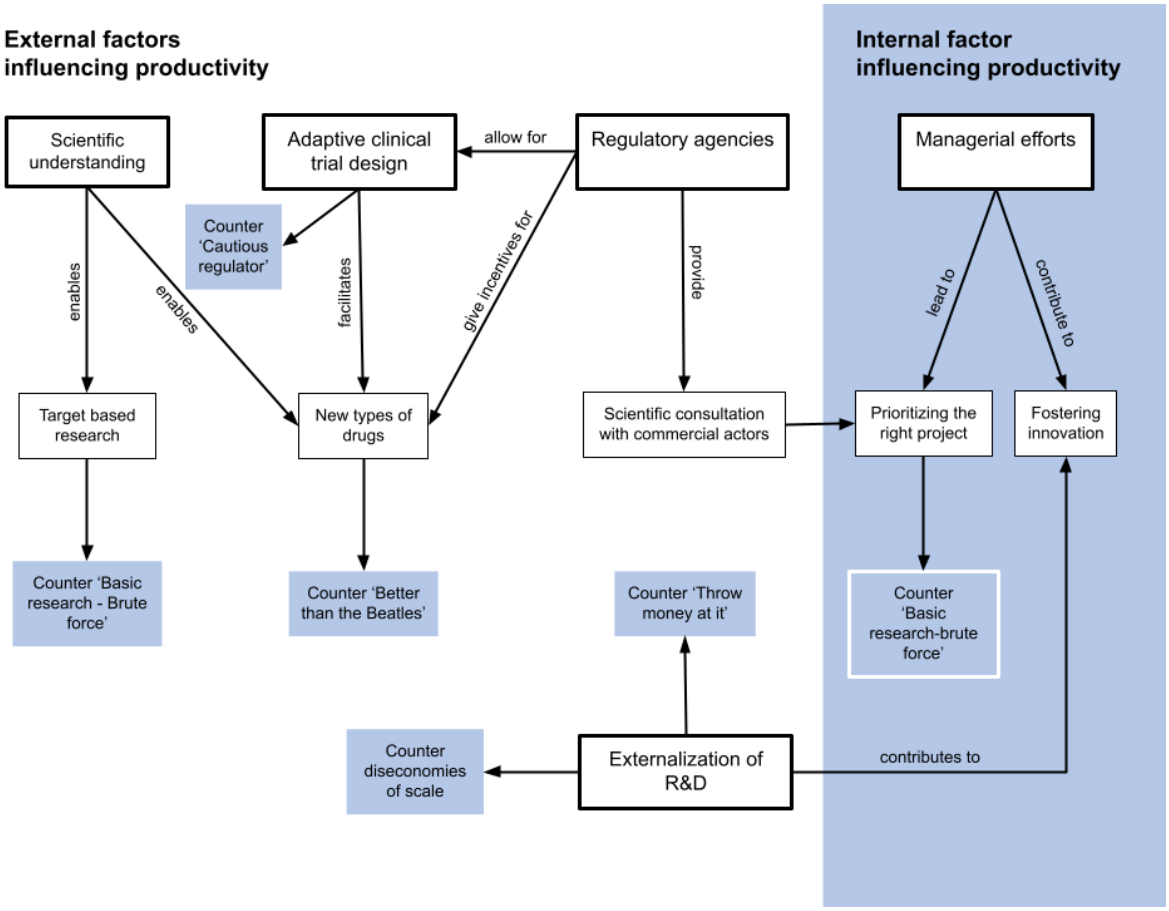
The interview study also reveals two other factors relevant to the R&D productivity increase, but which cannot be concluded as direct underlying factors. The importance of proper communication with regulatory agencies should by no means be overlooked, but the evidence suggests that it is rather a prerequisite for drug discovery and that the opportunities related to it have not changed considerably (5.3). When it comes to digital technology as a direct underlying factor for the turnaround, the scientific evidence provided by the results is insufficient to draw any conclusions (5.5).

In general, the literature study and interview study are well correlated. A more delicate analysis of particular cases where they conform or oppose is carried out in conjunction with the presentation of the interview study in chapter 5. However, it is important to note that all the six factors are inherently intertwined, and they influence each other in different ways as in an intricate network. The details and implications of this as further discussed in chapter 6. The discussion also touches upon the long-term durability of the proposed underlying factors (6.2), and the credibility of the results in terms of definitions used and apparent contradictions (6.3).

A visual representation of the qualitative findings from the study is presented in Figure 18 as a conceptual framework of the productivity factors and their intercorrelation. The figure can be seen as one of the major contributions of this study to the research on the turnaround of pharmaceutical R&D productivity.

Figure 18

A conceptual framework of the productivity network that was discovered in the study through qualitative research.



The presented conceptual framework is important because it provides a quick overview of the productivity landscape and can serve as a strong foundation for future research. For example, future studies could attempt to quantify the effect on the productivity of different factors to compare the relative significance of the factors. Another interesting aspect discovered in the study that can be further explored by future research studies is whether or not there exists a 'technology-brute force' bias in the industry as described in section 5.5.

The framework also reveals one of the most important conclusions from the results, which is that it may be difficult to quantify the factors separately as it shows how they are dependent on one another. With this interconnectivity, it becomes apparent that no single actor can change the productivity by itself, and that the industry must work together to further improve R&D productivity.

References

Adams, W.C. (2015). Conducting Semi-Structured Interviews. Handbook of Practical Program Evaluation. S. 492–505. https://doi.org/10.1002/9781119171386.ch19

Ascher, J., Bansal, R., Dhankhar, A., & Kim, E. (2020). *A new prescription for M&A in pharma.* McKinsey. Retrieved 2020 9 April from, https://www.mckinsey.com/business-functions/m-and-a/our-insights/a-new-prescription-for-m-and-a-in-pharma

Beg, S., Almalki, W.H., Malik, A., Farhan, M., Aatif, M., Rahman, Z., Alruwaili, N.K., Alrobaian, M., Tarique, M. & Rahman, M. (2020). 3D printing for drug delivery and biomedical applications. *Drug Discovery Today*. 25(9), 1668-1681. https://doi.org/10.1016/j.drudis.2020.07.007

Blomqvist, P., & Hallin, A. (2015). Method for engineering students: degree projects using the 4-phase model. Lund. Studentlitteratur.

Booth, B., & Zemmel, R. (2004). Prospects for productivity. *Nature Reviews Drug Discovery*, 3(5), 451-456. https://doi.org/10.1038/nrd1384

Bryman, A. (2011). *Samhällsvetenskapliga metoder*. (2., [rev.] uppl.) Malmö: Liber.

Cook, D., Brown, D., Alexander, R., March, R., Morgan, P., Satterthwaite, G., & Pangalos, M. (2014). Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nature Reviews Drug Discovery*, *13*(6), 419-431. https://doi.org/10.1038/nrd4309

Chan, H.C.S., Shan, H., Dahoun, T., Vogel, H., & Yuan, S. (2019). Advancing drug discovery via artificial intelligence. *Trends in Pharmacological Sciences*. https://doi.org/10.1016/j.tips.2019.06.004

Coccia, M., (2001). Tool for measuring the performance in the R&D organizations. *Italian National Research Council.* https://doi.org/10.1109/PICMET.2001.952291

Creative BioMart. (2013). A Summary of Characteristics of the Bio-pharmaceutical Industry. Retrieved 7 April 2021, https://www.creativebiomart.net/aboutus-detail-a-summary-of-characteristics-of-the-bio-pharmaceutical-industry-264.htm

Cuatrecasas, P. (2006). Drug discovery in jeopardy. *J Clin Invest*. 116(11), 2837-2842. https://doi.org/10.1172/JCI29999.

Cuatrecasas, P. (2009). Pedro Cuatrecasas. *Nature Reviews Drug Discovery*, 8(6), 446-446. https://doi.org/10.1038/nrd2906.

Davidson, B. (2018). How technology is helping improve the pharmaceutical industry. Retrieved 8 April 2021: https://percentotech.com/bobbyjdavidson/technology-pharmaceutical-industry/

Desai, N., Edwards, A.J., Ernest, T.B, Tuleu, C., & Orlu, M. (2020). 'Big Data' informed drug development: a case for acceptability. *Drug Discovery Today*. https://doi.org/10.1016/j.drudis.2020.12.011

DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics*, 47, 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012

Dowden, H., & Munro, J. (2019). Trends in clinical success rates and therapeutic focus. *Nature Reviews Drug Discovery*, 18(7), 495-496. https://doi.org/10.1038/d41573-019-00074-z

Dugger, S., Platt, A., & Goldstein, D. (2017). Drug development in the era of precision medicine. *Nature Reviews Drug Discovery*, *17*(3), 183-196. https://doi.org/10.1038/nrd.2017.226

Ellram, L.M. (1996). The use of the case study method in logistics research. *Journal of business logistics,* Volume 17, Number 2.

European Environmental Bureau. (2008). T*he Problem of Pharmaceutical Pollution.* Retrieved 5 May 2021, https://eeb.org/the-problem-of-pharmaceutical-pollution/#:~:text=The%20problem%20of%20pharmaceutical%20pollution%20Over%20100%2C000%20tonnes,other%20chemical%20ingredients%20are%20released%20into%20the%20environment.

European Medicines Agency. (2019). *EMA/FDA analysis shows high degree of alignment in marketing application decisions between EU and US.* Retrieved 11 May 2021, https://www.ema.europa.eu/en/news/emafda-analysis-shows-high-degree-alignment-marketing-application-decisions-between-eu-us

Fogel, D.B. (2018). Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. 11, 156-164. https://doi.org/10.1016/j.conctc.2018.08.001

Gold, E. R. (2021). The fall of the innovation empire and its possible rise through open science. *Research Policy, 50*(5), 104226. https://doi.org/10.1016/j.respol.2021.104226

Guarita, B., Belackova, V., van der Gouwe, D., Blankers, M., Pazitny, M., & Griffiths, P. (2021). Monitoring drug trends in the digital environment – New methods, challenges, and the opportunities provides by automated approaches. *International Journal of Drug Policy*. https://doi.org/10.1016/j.drugpo.2021.103210

Gupta, U., & Verma, M. (2013). Placebo in clinical trials. *Perspectives in clinical research.* 4(1), 49–52. https://doi.org/10.4103/2229-3485.106383

Granstrand, O. (2018) Industrial Innovation Economics and Intellectual Property (7th edition). Gothenburg: Svenska Kulturkompaniet.

Hall, J., Matos, S., Gold, S., & Severino, L. (2018). The paradox of sustainable innovation: The 'Eroom' effect (Moore's law backwards). *Journal of Cleaner Production*, *172*, 3487-3497. https://doi.org/10.1016/j.jclepro.2017.07.162

Hartford, A., Thomann, M., Chen, X., Miller, E., Bedding, A., & Jorgens, S. (2018). Adaptive Designs: Results of 2016 Survey on Perception and Use. T*herapeutic Innovation & Regulatory Science*. https://doi.org/10.1177/2168479018807715

Hayes, A. (2021). *Patent Cliff Definition*. Investopedia. Retrieved 7 April 2021, https://www.investopedia.com/terms/p/patent-cliff.asp#citation-1

Hennink, M. M., Kaiser, B. N., & Marconi, V. C. (2016). Code saturation versus meaning saturation: how many interviews are enough? *Qualitative health research*, 27(4), 591-608. https://doi.org/10.1177/1049732316665344

International Narcotics Control Board. (2010). *Drugs and Corruption.* https://www.incb.org/documents/Publications/AnnualReports/Thematic_chapters/English/AR_2010_E_Chapter_I.pdf

Jaruzelski, B., Loehr, J., & Holman, R. (2013). *The Global Innovation 1000: Navigating the Digital Future.* Strategy+Business. Retrieved 8 April 2021 https://www.strategy-business.com/article/00221?gko=92884

Karlsson, M., Trygg, L., & Elfström, B. (2004). Measuring R&D productivity: complementing the picture by focusing on research activities. *Technovation*, *24*(3), 179-186. https://doi.org/10.1016/s0166-4972(03)00111-1

Keeling, D., Lösch, M., & Schrader, U. (2010). *Outlook on pharma operations*. Retrieved 9 April 2021, https://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/operations/pdfs/outlook_on_pharma_operations.pdf

Klesty, V. (2010). Geely signs $1.8 billion deal for Ford's Volvo car unit. *Reuters*. Retrieved 11 May 2021, https://www.reuters.com/article/us-volvo-geely-idUSTRE62Q1F520100328

Kola, I. & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Review Drug Discovery.* 3, 711–716. https://doi.org/10.1038/nrd1470

Kuwashima, K., (2015). Exploring the Characteristics of Pharmaceutical Product Development. *Annals of Business Administrative Science*, 14(3), pp.161-170. https://doi.org/10.7880/abas.14.161

Laverty, H., Gunn, M., & Goldman, M. (2012). Improving R&D productivity of pharmaceutical companies through public-private partnerships: experiences from the Innovative Medicines Initiative. *Expert Review of Pharmacoeconomics & Outcomes Research*, 12(5), 545-548. https://doi.org/10.1586/erp.12.59

Lee, M., Ly, H., Möller, C., & Ringel, M. (2019). Innovation in Regulatory Science Is Meeting Evolution of Clinical Evidence Generation. *Clinical Pharmacology & Therapeutics*, 105(4), 886–898. https://doi.org/10.1002/cpt.1354

LIF. (2021). *Forskning och utveckling av läkemedel i Sverige*. Retrieved 14 Mars 2021. https://www.lif.se/statistik/forskning-och-utveckling-av-lakemedel-i-sverige/

Mahdavi, E. (2017). Patents and the Pharmaceutical Industry. *California Review Management.* https://cmr.berkeley.edu/2017/05/patents-and-pharmaceuticals/?fbclid=IwAR3G3mS0r1AorQYZd6XWYVV_KDNEHybhJunI2lEMJkW238YBXG6xwMWOpSM

Mahlich, J., Bartol, A., & Dheban, S. (2021). Can adaptive clinical trials help to solve the productivity crisis of the pharmaceutical industry? - a scenario analysis. *Health Economics Review*, 11(1). https://doi.org/10.1186/s13561-021-00302-6

Malterud, K. (2012). Systematic text condensation: A strategy for qualitative analysis. *Scandinavian Journal of Public Health*, 40(8), 795–805. https://doi.org/10.1177/1403494812465030

Malandraki-Miller, S., & Riley, P. (2021). Use of artificial intelligence to enhance phenotypic drug discovery. *Drug Discovery Today*. https://doi.org/10.1016/j.drudis.2021.01.013

Munos, B. (2009). Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery*, *8*(12), 959-968. https://doi.org/10.1038/nrd2961

Morgan, P., Brown, D., Lennard, S., Anderton, M., Barrett, J., & Eriksson, U. (2018). Impact of a five-dimensional framework on R&D productivity at AstraZeneca. *Nature Reviews Drug Discovery*, 17(3), 167-181. https://doi.org/10.1038/nrd.2017.244

Nosengo, N. (2016). Can you teach old drugs new tricks? *Nature*, 534(7607), 314–316. https://doi.org/10.1038/534314a

Pagliarulo, N. (2018). Novartis buys Endocyte for $2.1B in latest deal under CEO Narasimhan. *BioPharma Dive.* Retrieved 11 May 2021, https://www.biopharmadive.com/news/novartis-buys-endocyte-for-21b-in-latest-deal-under-ceo-narasimhan/540015/

Pammolli, F., Magazzini, L., & Riccaboni, M. (2011). The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery.* 10, 428–438. https://doi.org/10.1038/nrd3405

Pammolli, F., Righetto, L., Abrignani, S., Pani, L., Pelicci, P., & Rabosio, E. (2020). The endless frontier? The recent increase of R&D productivity in pharmaceuticals. *Journal Of Translational Medicine*, 18, 162. https://doi.org/10.1186/s12967-020-02313-z

Paul, S., Mytelka, D., Dunwiddie, C., Persinger, C., Munos, B., Lindborg, S., & Schacht, A. (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery*, *9*(3), 203-214. https://doi.org/10.1038/nrd3078

Pharmaceutical Technology. (2020). *The impact of big pharma on Covid-19*. Retrieved 7 April 2021, https://www.pharmaceutical-technology.com/comment/covid-19-pharmaceutical-companies-impact/

Pwc, (2013). *Managing innovation in pharma*. Pwc. https://www.pwc.com/gx/en/pharma-life-sciences/assets/pwc-managing-innovation-pharma.pdf

Réda, C., Kaufmann, E., & Delahaye-Duriez, A. (2020). Machine learning applications in drug development. *Computational and Structural Biotechnology Journal*, 18, 241-252. https://doi.org/10.1016/j.csbj.2019.12.006

Reichertz, J. (2010). Abduction: The Logic of Discovery of Grounded Theory. *Forum: Qualitive Social Research*, 11(1). https://doi.org/10.4135/9781848607941.n10

Ringel, M.S., Scannell, J.W., Baedeker, M. & Schulze, U. (2020) Breaking Erooms's law. *Nature Reviews Drug Discovery* 19, 833-834. https://doi.org/10.1038/d41573-020-00059-3

Saunders, B., Sim, J., Kingstone, T., Baker, S., Waterfield, J., Bartlam, B., Burroughs, H., & Jinka, C. (2018). Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant* 52, 1893–1907. https://doi.org/10.1007/s11135-017-0574-8

Sbernini, F., Granini, N., Lee Herbert-Hansen, Z.N., & Khalid, W. (2018). Contextual factors influencing the success of global product development. *International Journal of Product Development,* 22(6), 464-487. Retrieved 9 May 2021, https://www.researchgate.net/publication/328523151_Contextual_factors_influencing_the_success_of_global_product_development

Scannell, J., Blanckley, A., Boldon, H., & Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery*, 11(3), 191-200. https://doi.org/10.1038/nrd3681

Scannell, J. (2020, March 27). Life after Eroom's law. (J. Strident, Interviewer). Available on, https://refoundable.com/research/life-after-erooms-law-interview-with-jack-scannell.html

Scherer, F. (2000). Chapter 25 The pharmaceutical industry. *Handbook of Health Economics*, 1297-1336. https://doi.org/10.1016/s1574-0064(00)80038-4

Schuhmacher, A., Gatto, A., Hinder, M., Kuss, M., & Gassmann, O. (2020). The upside of being a digital pharma player. *Drug Discovery Today*, 25(9), 1569-1574. https://doi.org/10.1016/j.drudis.2020.06.002

Scopus. (2021). *Scopus Analyze Results*. Retrieved 11 May 2021, from https://www.scopus.com/

Statista. (2016). Outsourced research penetration in pharmaceutical industry worldwide from 2011 to 2020. Retrieved 5 May 2021, https://www.statista.com/statistics/813530/worldwide-share-of-outsources-research-penetration-in-pharma-industry/

Statista. (2020). *Global pharmaceutical R&D spending 2012-2026.* Retrieved 5 May 2021, https://www.statista.com/statistics/309466/global-r-and-d-expenditure-for-pharmaceuticals/

Stevens, H. & Huys, I. (2017). Innovative Approaches to Increase Access to Medicines in Developing Countries. *Frontiers in Medicine.* https://doi.org/10.3389/fmed.2017.00218

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. *Journal of Business Research*, 104, 333-339. https://doi.org/10.1016/j.jbusres.2019.07.039

The American Cancer Society. (2020). *Precision or Personalized Medicine.* Retrieved 8 April 2021, https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/precision-medicine.html.

Thomas, D. (2006). A General Inductive Approach for Analyzing Qualitative Evaluation Data. *American Journal of Evaluation*, 27(2), 237–246. Https//doi.org/10.1177/1098214005283748

Thomas, D., Chancellor, D., Micklus, A., LaFever, S., Hay, M., Chaudhuri, S., Bowden, R. & Lo, A.W. (2021). Clinical Development Success Rates and Contributing Factors 2011–2020. *Biotechnology Innovation Organization.* https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf?_ga=2.5035891.1556412080.1614422008-525948619.1614422008

Thompson, D., & Bentzien, J. (2020). Crowdsourcing and open innovation in drug discovery: recent contributions and future directions. *Drug Discovery Today*. 25(12), 2284-2293. https://doi.org/10.1016/j.drudis.2020.09.020

Tsai, W. & Erickson, S. (2006). Early-stage biotech companies: strategies for survival and growth *Biotechnology Healthcare*. 3(3),49-53. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571061/

Uddin, M. (2021). Blockchain Medledger: Hyperledger fabric enabled drug traceability system for counterfeit drugs in pharmaceutical industry. *International Journal of Pharmaceutics*. 597, https://doi.org/10.1016/j.ijpharm.2021.120235

United Nations. (2015). *The Global Goals.* Retrieved 210505: https://www.globalgoals.org/

U.S. Food and Drug administration. (2004). Innovation/Stagnation: Challenge and Opportunity on the critical Path to New Medical Technologies. World Health Organization. https://www.who.int/intellectualproperty/documents/en/FDAproposals.pdf

U.S Food and Drug Administration, (2018). The Drug Development Process. Retrieved 20 March 2021, https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

U.S. Food & Drug Administration. (2021a). *Exclusivity and New Drugs: What does it mean?* Retrieved 7 April 2021. https://www.fda.gov/media/111069/download

U.S Food and Drug Administration. (2021b). *Frequently Asked Questions on Patents and Exclusivity*. Retrieved 7 April 2021, https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#howlongpatentterm

Van Norman, G. (2017). Overcoming the Declining Trends in Innovation and Investment in Cardiovascular Therapeutics. *JACC: Basic to Translational Science*, 2(5), 613-625. https://doi.org/10.1016/j.jacbts.2017.09.002

Vetenskapsrådet. (2017). *God Forskningssed.* (VR 1708). https://www.vr.se/download/18.2412c5311624176023d25b05/1555332112063/God-forskningssed_VR_2017.pdf.

Virginia Tech. (2018). Research Methods Guide: Interview Research. Retrieved 8 April 2021, https://guides.lib.vt.edu/researchmethods/interviews

Wood, H. (2019). Pharmaceutical regulations and standards. Retrieved 7 April 2021, https://www.rentokil.com/blog/pharmaceutical-regulations/#.YG2NHC2l50t

Wouters, O.J., McKee, M., & Luyten, J. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*. 323(9), 844-853. https://doi.org/10.1001/jama.2020.1166

Zhou, S. and Johnson, R., (2018). Pharmaceutical Probability of Success. *Alacrita Consulting.* https://cdn2.hubspot.net/hubfs/3828687/Alacrita_April2019/PDF/Pharmaceutical-Probability-of-Success.pdf

Zhu, X., Li, H., Huang, L., Zhang, M., Fan, W., & Cui, L. (2020). 3D printing promotes the development of drugs. *Biomedicine & Pharmacotherapy.* 131. https://doi.org/10.1016/j.biopha.2020.110644

Appendix

A. Questions for interviewees in Swedish (original)

Vad anser du om effektivitet/produktivitet i läkemedelsforskning? Vad tycker du är viktiga mått för detta?

Hur har du sett arbetssätt påverkats och förändrats under de senaste 5, 10, 20 åren med koppling till effektivitet/produktivitet i R&D?

- Vilka tillvägagångsätt (såsom nya tekniker, metoder osv) har ni använt er av för att sänka kostnader?
- Hur ser du på förhållandet mellan mindre biotech bolag och Big Pharma bolag? Vilken roll ser du att M&As spelar för produktivitet?
- Arbetar man mot andra indikationer eller läkemedelstyper idag jämfört med 5, 10, 20 år sedan?

Hur ser du på framtiden? Kommer effektiviteten/produktiviteten minska, stagnera eller öka? Vad tror du är de största faktorerna att hålla ett öga på?

Vilken betydelse har regulatoriska myndigheter och hur påverkar de era val kring vilka läkemedel som utvecklas och era kostnader?

- Har ni kunnat identifiera någon förändring i regulatoriska krav eller interaktioner med regulatoriska myndigheter under de senaste 20 åren?
- Har regulatoriska förändringar lett till att nya medicinska områden blir lönsamma?

Hur förhåller ni er till "better than the Beatles' problem", det vill säga att det blir svårare och svårare att hitta ett läkemedel som är bättre än det som redan finns på marknaden?

Vilka är de största problemen ni ser inom läkemedelsindustrin för tillfället? Vilka är de största möjligheterna? Hur kan man komma förbi problemen?

Vilken fas är viktigast i avseendet finansiering? Finns det problem för företag att få finansiering idag?

Hur tror ni läkemedelsutveckling ser ut om 10-20 år? Liknande idag eller stora förändringar?

Är det något kopplat till ökande kostnader i R&D över tid som vi har missat? Eller något annat som du anser viktigt?

Har du något att tillägga som du inte tycker vi har behandlat?

B. Questions for interviewees in English (freely translated)

What is your take on the efficiency/productivity in pharmaceutical R&D? What do you think are important efficiency/productivity measures?

What changes have you seen to working methods in the past 5, 10, 20 years relating to R&D efficiency/productivity?

- What approaches (e.g., new technologies, new methods) have you used to reduce costs?
- What is your view on the relationship between smaller biotech companies and Big Pharma companies? What role do you consider M&As to have in relation to productivity?
- Are other indications or types of drugs pursued today compared to 5, 10, 20 years ago?

What is you take on the future of R&D productivity? Will it decrease, stagnate or increase? What do you think are the biggest factors to keep an eye on?

What is the significance of regulatory authorities and how do they affect your choices regarding which drugs to developed and your costs?

- Have you noticed any changes in regulatory requirements or interactions with regulatory authorities during the past 20 years?
- Have regulatory changes led to new medical areas becoming profitable?

How do you relate to "better than the Beatles' problem", that is, it becoming more and more difficult finding a drug that is better than what is already on the market?

What are the biggest problems in the pharmaceutical industry at the moment? What are the biggest opportunities? How can you get around the problems?

Which phase is most the important in terms of financing? Are there problems for companies to get financing today?

What do you think drug development will look like in 10-20 years? Similar to how it is today or big changes?

Are there anything linked to increasing R&D costs over time that we have missed? Or something else that you think is important to address?

Do you have anything to add that you feel we have not mentioned?

C. Sustainability and Ethics

The pharmaceutical industry, as well as the focus of this report, is heavily based on research and development whereas drug production comes in second hand. With that is also the sustainability topic predominantly focused on the ethical and social sustainability whereas environmental sustainability comes in second hand. Though, it can of course not be forgotten since it impacts the world we live in and that climate changes to some extent may impact the disease panorama as we see it today and cause a shift in what types of diseases the population will be battling in the future.

With the reasoning above and with the Sustainable Development Goals (SDG) stated by the United Nations (UN, 2015) as a foundation for this discussion, it can be said that sustainability is an important subject within the pharmaceutical industry and that many problems can be connected to the goals stated by UN. Moreover, the pharmaceutical industry has been characterized by diminishing R&D productivity since the 1950s, but in recent years, a positive trend shift has been observed (Ringel et al., 2020). The R&D productivity problem can be connected to SDG 8.2 to achieve higher levels of economic productivity through technological upgrades and innovation (UN, 2015). With higher R&D productivity, more drugs will be available for society, people will get less sick and thus be able to work more.

A higher R&D productivity will eventually lead to more people getting their medicine and more people on medication will lead to more waste. Therefore, an aspect to have in mind is waste management, how and where does the drug finally end up? Two SDGs highlight this problem, SDG 12.4 to achieve environmentally sound management of chemicals and all wastes throughout their life cycle, and SDG 14.1 to prevent and significantly reduce marine pollution in all kinds (UN, 2015). The production and consumption of pharmaceuticals play a significant role in the release of potentially dangerous chemicals, as studies show that between 30 to 90%, depending on the drug, of orally ingested medicine ultimately can be excreted through the urine production, thus cause leakages into the water (European Environmental Bureau, 2008). However, this becomes an ethical dilemma, whether the environment or human lives are worth more, which one should you focus on saving first? This makes the GDS contradict each other to some extent since more drugs will lead to better health of the worlds' population, but at the same time harm the environment. By taking the risk of further pollution into account when drafting strategies for the development of new pharmaceuticals such effects can hopefully be kept to a minimum.

Another goal addressed by the UN is Good Health and Well-being, which is listed as the third goal (UN, 2015). Within the third goal, two parts will be discussed, 3.3, Fight Communicable Diseases (CDs), and 3.4, Reduce Mortality from Non-Communicable Diseases (NCDs) and Promote Mental Health (UN, 2015). This goal is highly relevant to this study since R&D within the pharmaceutical industry is where the fight against diseases begins. To have a sustainable and productive R&D function would lead to new drugs coming out to the market and reducing the mortality rate from CDs and NCDs.

The results show that new ways of conducting clinical trials have emerged, which can make important drugs reach the market faster, and enabling research in areas where there have been difficulties before. However, a criterion about cost efficiency is included in the development of drugs, which means that drugs that could help society could be scrutinized before they reach the market, due to no willingness to pay. Regulatory agencies play a big role in where companies focus their R&D, by giving incentives to develop drugs in different indications. This also relates to goal 3.8 which targets the goal to provide effective and affordable medicine and treatments to all (UN, 2015). Developing countries are having big problems with communicable diseases and non-communicable diseases due to the high prices of drugs (Stevens & Huys, 2017).

There are many CDs and NCDs that probably could be treated and therefore partially solve goals 3.3 and 3.4, which leads back to goal 3.8, make it affordable for everyone. However, many attempts have been made to make the drugs more available for everyone, for example, subsidized drugs have been introduced to poor countries (Stevens & Huys, 2017). But then another problem arises, corruption. The biggest obstacle for international drug control is corruption and drug trafficking (International Narcotics Control Board, 2010). The corruption-problem is an issue that runs outside the scope of this thesis but is a very relevant problem to look at, to complete the goal of making drugs affordable and available to everyone. That being said, there are always different factors that affect each other, some more complex and harder to solve than others. This report focuses on the productivity of R&D within the pharmaceutical industry, and can therefore help solve goals 3.3, 3.4 and 3.8, by developing new drugs, however, the government must figure out a way to reduce corruption and make sure the drugs end up where they are supposed to.

There are also issues regarding ethics within the drug development process. One issue is the placebo-controlled trials, where some patients get treated with “sugar-pills” instead of the actual drug (Gupta & Verma, 2013). Gupta and Verma, (2013) explain that this is being done to prove a new drug’s effectiveness, where the researchers can compare the results between the placebo and non-placebo treatments. But is it ethically right to give a person in need, a sugar pill instead of giving them a chance with the new experimental drug?

There has been a discussion on whether this placebo method should be used or not since there are other ways of conducting the clinical trials, that would give results that are similar to the placebo-method (Gupta & Verma, 2013). There are also people saying that the placebo method is an important method to stop ineffective drugs from reaching the market, for example, Gupta and Verma (2013) that states: “is widely regarded as the gold standard for testing the efficacy of new treatments.” (p. 50).

To conclude, the results in the report give an understanding of the factors affecting the R&D productivity within the pharmaceutical industry. With this better understanding, companies within the industry hopefully can increase their productivity and hence get more, new drugs out on the market to help more people. As previously mentioned, the R&D is where the fight

against diseases begins, and it is crucial to have a working R&D function to contribute to the completion of the Sustainable Development Goals.

To complete goals 3.3, 3.4, and 3.8 a higher productivity within the pharmaceutical industry is essential but is however only one factor out of many that need to improve. For example, there is no point in delivering drugs to developing countries if the drugs do not end up where they are supposed to. It can be concluded that even though our thesis addresses important and relevant issues, it is impossible for one industry alone, to solve these problems.

On the other hand, a higher R&D productivity will lead to more drugs on the market and thus eventually more waste into the ocean and other water reservoirs. This counteracts the SDG 12.4 and 14.1. However, new, smart ways of handling waste will have to emerge, and hopefully, you will be able to solve one goal, without harming another.

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