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Challenges in the Swedish Drug Development Environment

- A qualitative study of the delay between preclinical and clinical trials

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Abstract

Based on yearly pipeline studies conducted by SwedenBIO in collaboration with Invest Sweden and VINNOVA, a transitional delay between late pre-clinical research and the initiation of clinical trials has been observed for a majority of micro- and small-sized pharmaceutical and biotechnology companies. The objective of this study was to identify the main forces being of particular influence to the early drug development process that could explain these observed delays.

Keywords

Drug development, pharmaceuticals, funding, innovation, competency, regulatory barriers

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CHALLENGES IN THE SWEDISH DRUG DEVELOPMENT ENVIRONMENT

- A qualitative study of the delay between preclinical and clinical trials

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Sammanfattning

Att framgångsrikt framställa ett läkemedel och lansera det på marknaden är en avancerad procedur som kräver många steg och processer. Bland annat måste innovationen vara effektiv och säker, finansiering måste kunna genereras, strategier måste utformas, och restriktionerna från olika marknader måste följas. För de större bolagen ligger problemet oftast i innovationsstadiet medan de yngre bolagen brottas med de senare utmaningarna i utvecklingsfasen. Studien "*The Swedish drug development pipeline*" (SwedenBIO, VINNOVA, Invest Sweden, 2006-2010) visar utvecklingen av svenska läkemedelsprojekt över åren där en tydlig fördröjning observeras för majoriteten av företagen, främst mindre läkemedelsföretag, i övergången mellan prekliniska studier och klinisk fas. Bakgrunden till denna studie ligger i just dessa observationer och syftet med undersökningen är att identifiera, genom kvalitativa intervjuer med sju representerande caseföretag, de krafter som främst utmanar produktutvecklingen i just den nämnda övergången i mikro och små läkemedelsbolag med utgång från fyra huvudsakliga omgivande faktorer innovation, finansiering, kompetens och regleringar.

This study has been conducted as a Master thesis by Sarah Wu from Uppsala University with the supervision from SwedenBIO. The report follows the basic structure designated by the University for students in the Molecular Biotechnology Engineering Programme. Apart from being available through SwedenBIO, the thesis can also be found through the Uppsala University thesis database. Sarah Wu has had the supervision of Karin Aase and Maria Kaaman from SwedenBIO and the scientific supervision from Göran Lindström, Uppsala University's department of engineering sciences - Industrial engineering.

Executive Summary

Pharmaceutical and biotechnology companies are facing rapid changes in their environment as the costs to develop new drug products increases and the number of approved drugs decreases. These are issues not only affecting the drug industry, but as well the entire Swedish healthcare. Despite being in the global top ten league of Life Science communities, most experts agree that the Swedish drug industry has lost a considerable part of its former brilliance. SwedenBIO has in collaboration with VINNOVA and Invest Sweden conducted an annual pipeline report that has been documenting the pipeline condition in Sweden since 2006. The results from this pipeline study have shown a transitional delay from late pre-clinical research to the initiation of clinical trials for a majority of the targeted companies. Based on literature, debates and other relevant sources, four main environmental factors were identified as being of particular influence to the early drug development process (preclinical to clinical trials) namely innovation, finance, competence and regulatory demands. In order to determine the impact of these environmental forces in the observed delay in micro- and small-sized pharmaceutical and biotechnology companies, statistical analysis and ten focused interviews were conducted. Seven case companies were studied that represented the commercialization of both small and large molecules in Swedish drug development companies.

When analyzing the results, financing – despite repeatedly making the headlines in recent years – was by the interviewees positioned on third place in the order of importance when discussing the factors affecting early drug development. It was also perceived to be solvable if the innovation and relationship between owners and other investors are handled appropriately. Regulatory demands were considered the least difficult when compared to the other three environmental factors. Although being rigorous and extensive, it is a necessity that all companies will pass as long as drug effect and safety is shown and operations follow protocol. The majority of the interviewees named the technical aspects of the innovation as the most important factor. But as emphasized by some, it is not whether the substance actually cures a disorder or not, it is about whether the market believes it cures the disorder or not and thus chooses to pay for it. If no one appreciates the implications offered by the drug, it can only be seen as a failure. Finally, competence and knowledge within the company was seen by the interviewees to be almost as important as the technical aspect of the innovation. Since most pharmaceutical and biotechnology companies today employ no more than fifteen employees, it becomes extra important to have the right combination of knowledge internally to manage the indispensable virtual network that help maintain operations.

Based on these findings, it was confirmed that the four theoretical environmental factors identified were the forces most influential in the success and failure of a drug project in its early development stages. Although having been given different reasons explaining the observed delay between preclinical research and clinical trials, one common denominator could still be deduced. In all parts of the earlier operational activities, the internal competence of the company was shown to be of upmost importance. In order to make the original discovery marketable the company needs to understand both the basic research behind the innovation as well as the appropriate measures to strengthen its market appeal. By having competent and experienced drug developers internally a small company could better manage the use of external knowledge and labor to perform the necessary development activities. Finding and ensuring funding and partnering deals were made simpler if the employees within the pharmaceutical and biotechnology company have the competence of marketing and communicating its ideas and strengths. The owners need confirmation that investment is safe and worthy, and potential future partners needs to see that everything done so far has increased the value of the original invention and that the project at hand will be profitable for all parties involved. Despite the order of importance given by the interviewees, competence has been singled out to be the most important factor for micro- and small-sized pharmaceutical and biotechnology companies in early development stages when taking all these aspects into consideration.

Table of contents

1 Introduction

1.1 Background

For the past several years, the global drug industry has been facing an unprecedented crisis with the number of drugs approved being the lowest in the history of the industry. At the same time, the cost to discover and develop has increased exponentially and shows no signs of slowing down (Owens, 2007). These are issues of great concern, not only for the industry itself, but also for the entire global healthcare. Long-recognized diseases, such as

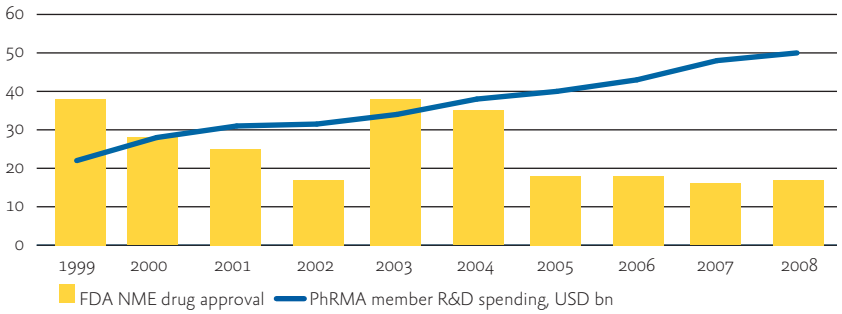

Exhibit 1. The productivity vs. spending of the pharmaceutical industry from 1999–2008, American data. FDA NME: US Food and Drug Administration New Molecular Entity. PhRMA: The Pharmaceutical Research and Manufacturers of America (represents the country's leading pharmaceutical researc and biotechnology companies). *Source: Karolinska Development, 2009.*

Cancer and Alzheimer's are becoming more and more common as a greater proportion of the world's population reaches old age. Previously established disorders such as AIDS and obesity as well as recent threats from the H1N1 flu are constantly emphasizing the risks of new perils (Barden et al., 2009). Thus, it is clear that it is imperative to take steps towards a high productivity drug development process in order to address both these and other global health issues.

The Swedish drug industry has been in a world-leading position for almost a hundred years. With well-known corporations such as Pharmacia, established 1911, and Astra (now AstraZeneca) established 1913, a high standard has been set on Swedish drug development. The Life Science business sector (including pharmaceuticals, biotechnology and medical technology as defined by VINNOVA) is today as extensive as ever with more than 30 000 employees in around 600 companies (Sandström et al., 2007). A majority of these are in the dealings of discovering, producing or developing drugs (SwedenBIO, 2006). But even though the performance of the Swedish drug industry has managed to stay amongst the top ten in the world, we still face the same challenges as everyone else. The increased time needed for dis-

covery and development, the decreased innovative strength of Big Pharma[1] companies, and stricter regulatory demands from authorities, are all important concerns affecting the industry, craving prompt attention both globally and locally, see exhibit 1 (Kola, 2008). Today, most experts agree upon the fact that the Swedish drug industry has lost a considerable part of its former brilliance (Arvidsson et al., 2007). This awareness and concern has also been reflected in the amount of studies[2] conducted in recent years on how to boost the Swedish drug development environment in order to increase its appeal and success. Since it is widely recognized that a fruitful Life Science industry is directly related to high standards in our healthcare environment, its prosperity should be considered a societal priority (Arvidsson et al., 2007).

One of the market analysis surveys conducted yearly document the pipeline condition in Sweden and dates back to 2006. It is carried out by SwedenBIO – the Swedish Life Science industry organization – in collaboration with Vinnova and Invest Sweden. In these surveys, around 200 projects in total have been recorded throughout the years in terms of targeted disease, type of molecule (small/big), state in development process et cetera. These data, when statistically analyzed, shows a transitional delay from late pre-clinical research[3] to the initiation of clinical trials for a majority of the companies. Based on literature, debates and other relevant sources, four major environmental factors were identified as being of particular influence to the early drug development process (preclinical to clinical trials). By getting a better and deeper understanding of how these are met by different players in the industry, a more lucid image of the forces surrounding and affecting companies today may be portrayed, allowing us to search for more appropriate measures when working to strengthen the Swedish drug industry.

1 Large pharmaceutical companies that generate more than $2 billion a year, have international operations, have research and development (R&D) in at least five different therapeutic areas and are fully integrated including R&D, manufacturing, clinical, regulatory, marketing and sales operations (Rosen, 2005).

2 E.g. Arvidsson et al. 2007 "Medicin för Sverige! – nytt liv i en framtidsbransch", Stendahl, O. 2008 "Klinisk forskning – ett lyft för sjukvården", Vinnova 2009 "Internationellt jämförande studie av innovationssystem inom läkemedel, bioteknik och medicinteknik" etc.

3 Definition: less than one year to intended clinical trial initiation.

1.2 Objective of the study

The objective of the study is to determine the impact of the main environmental forces responsible for the observed delay in drug development between late preclinical stage and the initiation of the first clinical trials in micro- and small-sized pharmaceutical and biotechnology companies.

1.2.1 Delimitations

Owing to the fact that the majority of Swedish pharmaceutical and biotechnology companies consist of less than 50 employees as deduced by VINNOVA, this study has been limited to include only micro- and small-sized organizations[4]. Another delimitation is the selection only of case companies that has participated in SwedenBIO's annual pipeline survey. The validation of conclusions drawn from the surveys (2006–2009) should appropriately be based on the companies involved. Finally, when discussing pharmaceutical and biotechnology companies within this study, I choose to limit myself to only include drug discovery and development companies as well as drug delivery companies as defined by Vinnova[5] due to their similarities and thus comparability in drug development characteristics.

1.3 Disposition

The report is structured into six main chapters with a few subsections each to make it easier for the reader to grasp the contents. In the initial chapter, the background of the study is presented and the objective stated along with the delimitations. The second chapter provides the reader with an overview of the Swedish Life Science industry up to date and briefly explains the drug development process. An account of the methods used throughout this study is presented in the third main chapter. The fourth chapter comprises statistical data attained in the earlier stage of analysis and summerized characteristics of the case studies. Finally, the analysis is accounted for in the fifth chapter followed by the conclusions and discussions in the sixth chapter. References and supplements, such as interview questions and neutral recollections of each case study, can be found in the last part of the report.

4 Micro enterprises are defined as having 1–10 employees, small enterprises are defined as having 11–50 employees.

5 The character of each category is shown in chapter 2.2.

2 The Swedish Life Science industry

2.1 Once Upon a Time There Was Astra

The 14th of February 1913 is by many people seen as the starting date of a new Swedish large-scale industry, namely the pharmaceutical industry. The headlines in Dagens Nyheter, a daily newspaper, that day auspicated a bright future for the first Swedish drug manufacturing company ever. Accordingly, the first couple of years went as planned, but the growth never really took off as anticipated. Instead, the company came close to a bankruptcy following the crisis of The First World War. Forty years later, after a number of reorganizations, what is to be known today as Astra AB had finally been able to meet earlier expectations and successfully increased its turnover a hundredfold. At that time, other Swedish Life Science companies had also established themselves on the market, one of these being the well-known Pharmacia (LäkemedelsVärlden, 2002). During the following decades, newly innovated drugs and medical technologies facilitated Astra and Pharmacia's continuous expansion. But it wasn't until the 1980's that these two companies launched the products that made the Swedish Life Science industry what it is today, setting a high standard on Swedish innovations and healthcare structures (Affärsvärlden, 2005).

Over the years, the drug sector in Sweden has transformed from a few large players into a complicated mixture of mainly micro and small-sized companies, making up for around 7 % of the total Swedish net export value (SwedenBIO, 2007; SCB, 2010). Pharmacia has become part of the world's largest Big Pharma, Pfizer, and is no longer mentioned amongst its development facilities. Astra on the other hand merged with the British Zeneca in 1999 creating AstraZeneca, its head quarter now located in London. Although Sweden is still listed amongst the top ten international drug development communities, most industry experts agree that there are significant reasons to worry about the future development. There has during these last two decades been a noticeable lack of newly developed products capable of replacing some of the blockbuster drugs[6] launched more than twenty years ago. Astra's *Losec* (1988) and its sequel *Nexium* (2000) are still the drugs that have generated the most revenue, reaching total sales of 6.5 billion USD a year (Arvidsson et al., 2007).

Despite major reorganizations, AstraZeneca continues to dominate the Swedish drug industry, employing one fourth of all workers within Life Science related activities. Its products, accounting for 50 % of the Swedish drugs

6 A drug that generates over $1 billion each year.

export value, awaits expiring patents within the following four years (Arvidsson et al., 2007; Swedish Trade Council, 2010). So what does the future behold for us? According to Barden and Weaver (2010), a "new ecosystem" with the younger micro enterprises in the lead might be the answer. Kaitin (2010) further argues that small pharmaceutical and biotechnology companies are less encumbered by functional silos, making them better able than Big Pharma to focus on emerging technologies, and many experts and authorities agree (Barden et al., 2010; Kaitin, 2010; Burrill & Company, 2010; Ernst & Young, 2009; European Commission, 2009). They are as indicated much smaller in size, but their numbers are constantly increasing. If the right opportunities are identified and grasped, these highly innovative groups could bring significant potential to the future of the industry.

2.2 The Characteristics of Life Sciences in Sweden

Each of the companies included in this study may be characterized into at least one of three overlapping sectors depending on their main business activities, namely pharmaceuticals; biotechnology; and medical technology. Together, the three sectors constitute the Life Science industry, as we see it today. In this thesis, focus has been put on companies included in the pharmaceutical and biotechnology sector working with either conventional or biopharmaceutical drug discovery, development and delivery. Apart from these activities, therapeutic products; therapeutic methods; and production are other operations also included in the two sectors, but not considered in this study. Medical technology on the other hand includes the development of medical products that are not drugs, such as healthcare equipment and medical devices. This sector is not further discussed in this report. It is important to note the interconnectedness between pharmaceutical and biotechnological businesses, since the correct usage of these terminologies is rather vague. For instance, there are many companies within drug discovery that could be defined neither as exclusively part of the pharmaceutical nor of the biotechnology sector (Sandström et al., 2007; OECD, 2010). Another way to differentiate Life Science companies is through business segments also defined by VINNOVA. This study will, as mentioned above, only take into account companies fitted into the two business segments: drug discovery and development, and drug delivery. The drug discovery and development segment include pharmaceutical and biotechnology companies researching and developing new drugs and therapies, while the drug delivery segment include companies that focus on the delivery and the uptake of target substances in the body.

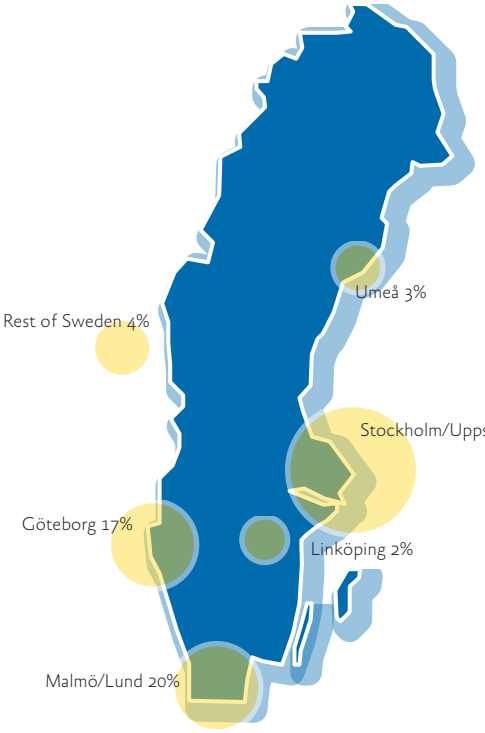

Exhibit 2. The geographical distribution of companies within the Life Science industry in Sweden, 2006. *Illustration used with the permission from Sandström, VINNOVA.*

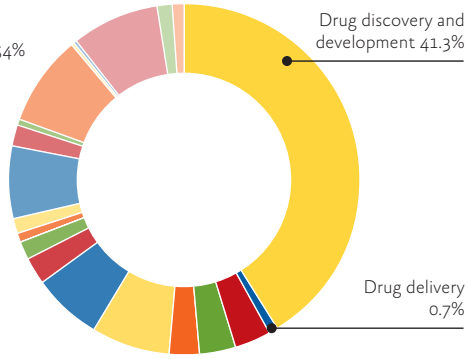

Exhibit 3. The distribution of employees amongst business segments within the Swedish Life Science industry 2006 (Marketing and sales not included). *Source: Sandström et al. 2007.*

The five most prominent Life Science regions in Sweden are, as shown in exhibit 2, Stockholm/Uppsala; Malmö/Lund; Göteborg; Umeå; and Linköping. Outside of these cluster regions, none of the few remaining companies are research-intensive. Stockholm is the center for drug discovery and development businesses in Sweden and has a majority of pharmaceutical companies. In Uppsala on the other hand, a more assorted group of biotechnology and medical technology companies reside, largely due to Pharmacia's earlier activities in the area (Sandström et al., 2007). As mentioned in the previous chapter, a majority of the 600 companies in Sweden are smaller businesses and commonly situated in clusters within different Science Parks in close proximity to one of the country's six university hospitals (UNIONEN, 2008). According to Vinnova, more than 30 000 people in Sweden[7] are presently working with Life Science related activities. 41.3 % of these could be characterized into the drug discovery and development segment. The rest are more or less evenly spread out amongst other fields of core operations, see exhibit 3. Between 1997 and 2003, the industry has in total grown with more than ten thousand employees in which the micro and small-sized companies are largely responsible. However, during 2003 to 2006, no major changes have occurred (Sandström et al., 2007).

7 Data is from 2006. Marketing and sales activities are not included.

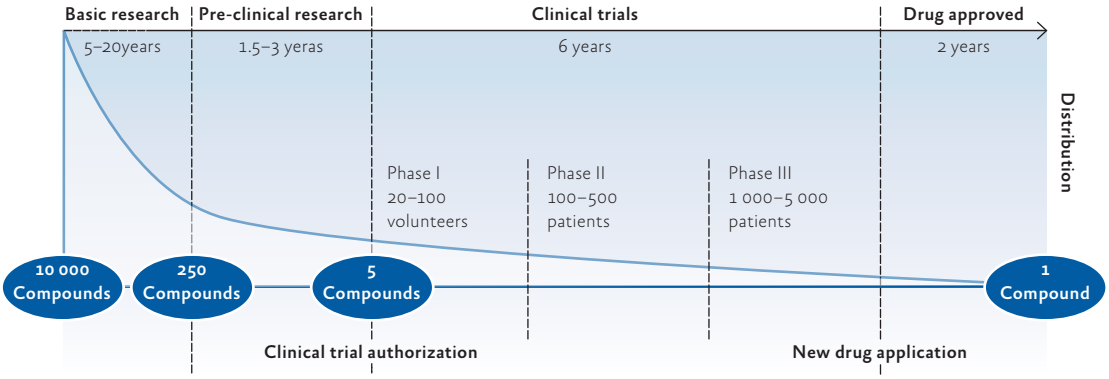

Exhibit 4. The drug development process from discovery to distribution generally involves basic research, pre-clinical research and three phases of clinical trials. Only one out of ten thousands discovered substances is according to statistics approved for market entry at least 10 years after identification. NB. This is a simplified schedule of the process and many different versions and timelines rotate amongst experts. There are also considerable variations among different therapeutic areas. *Illustrated by the author based on: SwedenBIO (2009), MPA (2010), The Swedish Ministry of Enterprise, Energy and Communications (2005).*

2.3 From Discovery to Approval

The first step in the drug discovery and development process is for researchers to identify a substance, either a chemical substance (small molecules) or a biopharmaceutical substance (large molecules) that has the ability to affect the behavior of a certain disorder. This target substance is then characterized and chemically modified to express the desired characteristics (AstraZeneca, 2010). Typically, this stage in smaller companies is partly performed within the academy (SwedenBIO, 2009). In the following pre-clinical phase, the target substances that show theoretical and in vitro potential is examined on animal models and pharmacokinetic tests are carried out to confirm effectiveness. At the same time, toxicology trials are conducted to verify the frames of safety for the substance. After gathering enough data for an approval from the Swedish Medical Product Agency (MPA) – a critical stage in drug development – clinical trials are set up to be initiated (AstraZeneca, 2010). Again, in the case of the smaller companies, the pre-clinical activities are either performed in the academy or in the company that will be responsible for the continued development, or in both (SwedenBIO, 2009).

There are three phases of clinical trials to surmount before the new drug application (NDA) is due for submission. The first Phase I trial (CT I), also known as the first trial in humans, is conducted on healthy volunteers with the purpose of deciding the range of dosage application. These studies are also performed to understand the metabolism and physiology of the drug versus human interaction. Possible side effects are identified and recorded throughout all phases (Lemne, 2004). In some cases, the CT I trial may be divided into two sub-trials, Ia and Ib, in which the Ib trial is performed on

a small group of patients instead of healthy volunteers (Medivir, 2010). The timeframe for a first clinical trial is generally 1–1.5 years when including documentations and other extracurricular activities (Active Biotech, 2010). Although it should be noted that the timeframes and development stages as described here and in exhibit 4 is only one of many interpretations. The exact timings and setup varies from project to project (AstraZeneca, 2010).

Phase II (CT II) differs from Phase I by including patients with the purpose of deciding the dosage versus effect relationship. These patients are often selected as homogenously and healthy as possible apart from the targeted disease. The CT II is often divided into a IIa and a IIb trial. According to Karin Meyer-Rosberg, Managing Director at Quintiles Sweden, this is to confirm the success potential as early as possible. A Phase IIa trial is often referred to as a proof of concept in humans and is apart from the inclusion of patients similar to a Phase I trial. Phase IIb trials are often larger studies in which the most appropriate range of dosage application is investigated and defined for continued investigation in Phase III trials (Nordic Life Science Review, 2009). A CT II is expected to run for 1.5–2.5 years (Active Biotech, 2010).

The third clinical trial (CT III) is sometimes referred to as confirmations studies and the most rigorous and extensive part of the development process. Here, the purpose is to document the effect of the drug substance on a heterogenic group of patients often consisting of 1000 to 5 000 people. The estimated timeframe varies between 2–4 years. Different alternative studies are commonly conducted to satisfy the deviations in legislation in different countries in order to obtain a local NDA approval. Once finishing the Phase III trial, all documentations are gathered and a NDA is submitted in order to bring the drug onto the market. If approved, a fourth phase clinical trial called non-intervention studies is initiated after market entry. These trials are often conducted to gain knowledge of the long-term effects of the drug as well as the rarer side effects (Lemne, 2004).

Few substances identified as potential drugs make it through the whole process. According to a study conducted by DiMasi et al., the probability of a drug candidate entering CT I to reach the market is 16 %[8]. Once the first trial is successfully completed, the chance of success improves to 26 %[9] as can be seen in exhibit 5. Finally, the likelihood for a CT II approved drug

8 The mean value of self-originated and licensed-in probabilities. US data.

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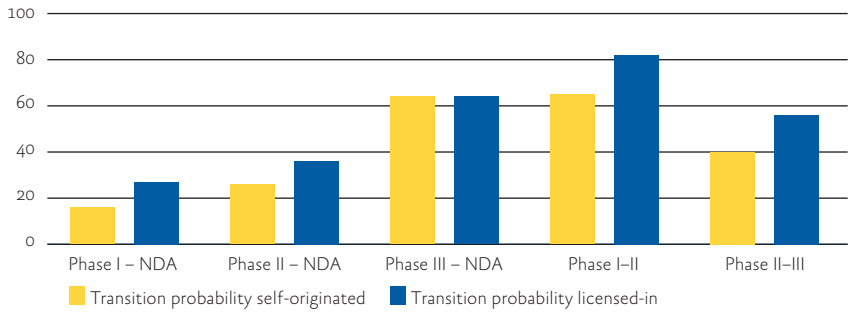

Exhibit 5. Phase transition probabilities and clinical approval success probabilities based on compounds first tested in humans from 1993 to 2004 in the US. NDA = new drug application. *Source: DiMasi, 2010.*

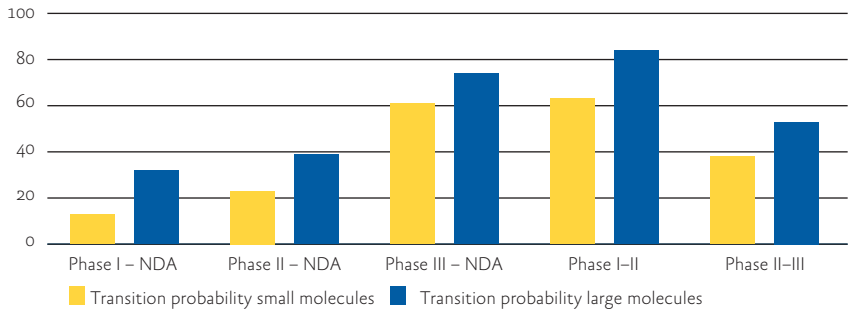

Exhibit 6. Phase transition probabilities and clinical approval success probabilities based on compounds first tested in humans from 1993 to 2004 in the US. NDA = new drug application. *Source: DiMasi, 2010.*

candidate to reach an NDA submission is estimated to be 64 %[10]. As shown in DiMasi's article (2010), large and small molecules demonstrate variations in terms of transition probabilities, which can be seen in exhibit 6. Low success rates coupled with long development times leads to high overall R&D costs for the research-based industry. According to Kaitin (2010), a recent Tufts CSDD study (Tufts Center for the Study of Drug Development) showed that the average cost to bring one new biopharmaceutical product to the market, including the cost of failures, is $1.24 billion in 2005 dollars. The same cost for conventional pharmaceuticals is $1.32 billion (Kaitin, 2010). In Europe, the estimated costs for development are even higher still; partly due to the fragmented European patent system increasing the intellectual property (IP) costs eleven fold in comparison to US patents (European Commission, 2009; European Commission, 2010).

10 The mean value of self-originated and licensed-in probabilities. US data.

2.4 Elements in the Theoretical Equation of Efficiency

In this study, the initial theoretical model include four elements that are continuously brought up in reports from organizations such as Burrill & Company (2010) and Ernst & Young (2009), namely funding; innovation; competence; and regulatory barriers. These forces are often described in association to important issues impacting the drug industry. As indicated by Burrill & Company, these are the elementary environmental factors that have the power to both incite and limit the industry climate today. The specifics of each element are further discussed in the following subchapters.

2.4.1 Funding

The worldwide financial crisis, producing the most headlines for the past two years, continues to cause global economic decline affecting especially developed countries. This environment leaves more room to companies with products and revenues posing lower risk to the investor, and less to early-stage development companies (Burrill & Company, 2010). The shareholders that the smaller players in the industry have come to rely on – venture capitalists (VC), public investors and Big Pharma – will according to Ernst & Young (2009) predictably face constraints of their own that might limit their commitment. The VC funding model has come under unprecedented pressure with the financial crisis; increased duration to exits; increased regulatory uncertainties; and lower returns from initial public offerings (IPOs). At the same time, the public investors are not expected to return any time soon, leaving the small public companies with a lesser amount of capital (Ernst & Young, 2009). A third change in the funding environment for smaller companies is the increased constrains of Big Pharma investments predicted by Ernst & Young due to their focus on integrating mega-mergers and reduced investments in research and development (R&D). Despite the need for newly innovative products from external sources to fill the gap in their pipeline, there will be less motivation to invest in more than what is absolutely necessary (Ernst & Young, 2009). *"As for now, it costs US$1–2 billion to build a sustainable enterprise, and there will simply not be enough capital to sustain a large number of today's companies at that level"* (Ernst & Young, 2009).

2.4.2 Innovation

With the upcoming dwindling revenue streams due to blockbusters going off patent over the next five years, both larger Big Pharma and smaller pharma-

ceutical and biotechnology companies request new innovative replacements. The question is how these new innovative replacements are to be identified. For many years, drug makers have sought to find "best-in-class" drugs in which the product is superior competitors' in terms of efficiency, safety and other features. These differentiating drugs have generated the most value creation in firms in the past (Booth et al., 2003). But according to Frank, the vice chairman of the investment-banking firm Peter. J. Solomon Company, "first-in-class" drugs – a new medicine with a new mechanism developed into a new area – is what will be the new "best-in-class" in the future (Burrill & Company, 2010). Two experts at the PA Consulting Group agrees with Frank in a letter published in The Times this year, stating that the future of pharmaceuticals and biotechnology no longer lies in blockbuster drugs, but in niche products. However, they also observed a paradox in the situation that these drugs, being much more expensive to develop but at the same time target fewer patients than blockbuster drugs, might make it uneconomic for the originator to maintain production after patent expiration. This in return could increase the difficulty of justifying innovation in the long run (Dams et al., 2010).

Only discussing innovations in terms of drug efficacy and safety is according to Rothwell et al. (1974) not enough. Based on finding from the SAPPHO project, in which an attempt to discover the differences between successful and unsuccessful innovations were presented, the research and development (R&D) of an invention[11] is shown to be *"a priori condition for entering the race rather than a factor in success or failure"*.It is further stated that other factors such as the understanding of customer needs, attention to marketing and publicity, efficiency in development (but not necessarily speed), and the corporate competence are areas in which success and failure is distinguished (Rothwell, 1974).

2.4.3 Competency

This element encompasses the strategic direction as well as the use of knowledge within companies. Since Big Pharma is constrained by financial and market concerns that direct the product discovery and development, an emphasis is put on speed instead of originality. The smaller companies on the other hand, often stemming from academic institutions, have been able to devote more time and effort on the innovative sides of drug development resulting in advanced technology and creative solutions (Ernst & Young, 2009). Hence, the old business model in which Big Pharma apply the one-size-fits-all solu-

11 Innovation is an invention that has been taken up and commercially developed (Roberts, 1998).

tion is now part of the past, and a new ecosystem, as described by Barden and Weaver, is becoming the current vogue. In this new ecosystem, new relationships between a network of stakeholders is formed in which micropharma, defined as mainly academia-originated start-up companies that are efficient, flexible, innovative, product-focused, and small, hold a key position. As a result, virtual enterprises and complex value-chains are new structural challenges for those involved. In order to uphold productivity and sustainability in this new ecosystem, appropriate business strategies and competencies must be developed. Participating in micro ventures must not be business-as-usual for the academic researcher and thus knowledge and competence is of utmost importance. The smaller the company, the more crucial it becomes to have the right competency in order to confront new challenges. An understanding for translational research and the development of useful and beneficial products is essential (Burrill & Company, 2010; Barden et al., 2010).

2.4.4 Regulatory environment

Burrill & Company predicts that the regulatory world will become more complex, following the inclusion of comparative effectiveness research into the equation. It is no longer enough to simply tell if a new drug candidate is effective and safe, it now has to provide greater value over existing treatments in order to be approved. The government involvement will according to Burrill & Company also increase and create new arrays of regulatory and compensatory rules, issues, and challenges for Life Science companies. Government healthcare programs such as the US-based Medicare and Medicaid will play greater role in the delivery and reimbursement of healthcare worldwide (Burrill & Company, 2010).

In Europe, the fragmented patent system continues to give rise to unnecessary costs for those involved. There are two contemporary issues frequently discussed in association with the current European patent system namely the costs for translation and the decentralization of the court system. Since each European market needs its own patent application in its own language and each patent dispute is put on a domestic level with its own set of laws and procedure, costs and effort skyrocket. Therefore, the development of a uniform system will indisputably lead to new opportunities (European Commission, 2010).

3 The methodology

This empirical research study was conducted using both primary and secondary data and in the explanatory form as defined by Riley et al. (2002) to be *"directed towards exploring the relationships between concepts and phenomena and explaining the causality and/or interdependency between these"*. The design of the study follows the characteristics of a simplified multi-case strategy with data from semi-structured interviews on seven case companies and secondary sources. According to Yin (2002), *"case studies are the preferred study when "how" and "why" questions are being posed, when the investigator has little or no control over the events, and when the focus is on a contemporary phenomenon within some real-life context"*. Hence, the case design is considered the most appropriate method to use in this study.

3.1 The Swedish Drug Development Pipeline Analysis

SwedenBIO is an industry organization established 2003, by members from seven Swedish Life Science companies with the objectives to support, promote, and foster the Swedish life Science sector. The organization works to strengthen the voice of its member companies and act as the platform for knowledge distribution, networking and relationship building. SwedenBIO has 190 members within the business of Life Sciences and secondary companies providing different kinds of services for this industry.

The Swedish Drug Development Pipeline is a survey conducted every year by SwedenBIO in cooperation with Invest Sweden and VINNOVA dating back to 2006. The results serve as a quantitative indicator to the progress of Swedish pipeline projects and their characteristics. The report has evolved throughout the years and the number of participants has increased from 39 companies 2006 to 58 companies 2009. Due to mergers, acquisitions, liquidations and other explanations, some companies have only been registered one or two years. The data has mainly been collected through Internet surveys and analyzed thereafter.

The target selection for the pipeline study was primarily based on a list of companies provided by VINNOVA, Invest Sweden and SwedenBIO, in which only Swedish-based research and development (R&D) companies were included (i.e. no marketing and sales companies). Also, only companies primarily working with drugs and therapies of some kind were surveyed. Secondly, it targets companies with active project in the late preclinical stage (less than one year to first clinical trials) and clinical trials at the time of conduct. Out of these companies, 69 were approached in 2006; 77 in 2007;

79 in 2008; and 90 were approached in 2009. The final average response rate achieved was 91 %. This study does not include data from the 2010 pipeline survey, since it had not yet been finalized at the time of the research. Instead, corporate homepages were used to gather more recent information.

3.2 The Statistical Research Study

Prior to the initiation of this thesis, SwedenBIO requested an aim to focus on the issues related to the transition of drug development from late preclinical stage to the first clinical trials. In order to determine and analytically conclude that the objective was relevant and significant, a statistical study was performed after a first selection.

3.2.1 The 1st selection

To ensure the significance and reliability of the study, a first sample was systematically selected from the dataset obtained in the four *Swedish Drug Development Pipeline* reports from 2006–2009 including all data satisfying the following criteria (Bryman et al., 2005).

Select only companies:

- that has participated in The Swedish Drug Development Pipeline survey for at least two years.
- defined as either being in the Drug discovery and development segment or in the Drug delivery segment.
- with at least one project fully reported (e.g. project name, targets, development stages etc.).
- with the strategy to enter clinical trials.

Information concerning the current condition of the companies and their projects were gathered from corporate homepages, annual reports and press releases. The resulting selection consisted of 42 companies with a total of 143 reported projects. These data were then used to perform a statistical analysis of the drug development progression in Sweden 2006–2010.

To be able to follow the progression of each company's product development, more than two years of data must have been recorded to gain relevancy. Also, in order to allow comparison between each separate project, their

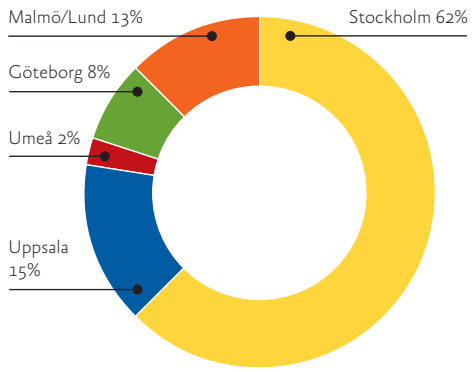

Exhibit 7. The distribution of companies included in the first selection amongst Sweden's top five Life Science regions.

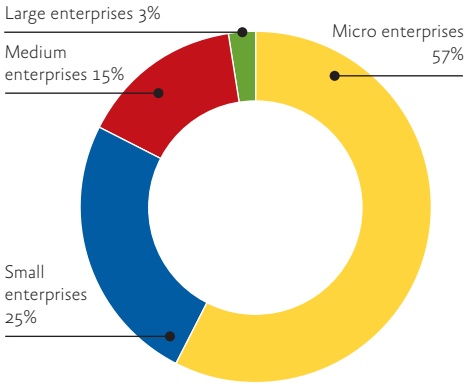

Exhibit 8. The size-distribution of the representing companies included in the first selection.

overall development process must be similar, hence the inclusion only of drug discovery and development and drug delivery projects. Criterion three and four is to discriminate the most reliable data available and minimize possible selection errors. In exhibits 7–9, the characteristics of the first sample is shown in terms of headquarter region, corporate size and the type of molecule developed.

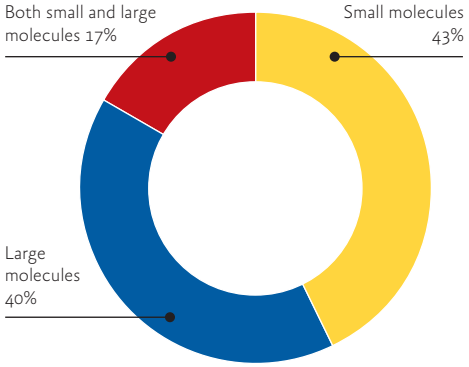

Exhibit 9. The type of molecules each representing company included in the first selection develops.

3.2.2 Method used for statistical research

The statistics were calculated after the compilation of data from 42 companies and 143 projects, earlier included in the *Swedish Drug Development Pipeline* reports (2006–2009). These data were then supplemented with secondary information from annual reports, corporate homepages and press releases. The final data set included the name of the company; the preliminary project name; the proposed target indication; the type of molecule involved; and finally, the number of year spent in each phase of development (late preclinical, CT I, CT II, CT III) from 2005–2010. The statistical setup was calculated in MS Excel and the conclusions drawn from these are shown in chapter 4.1.

3.3 The Case Study

The conclusions drawn from the secondary data and statistical analysis were used when sampling the second dataset of this study. The research design has followed the structure of a case study as defined by Yin (2002) with a study question, a study proposition, the units of analysis, the linking of data to propositions, and finally the criteria for interpreting the findings.

3.3.1 The 2nd selection and the research design

After concluding that the statistical data obtained in the premier phase of research indicated the same observations made earlier by SwedenBIO, a second selection was performed to determine the case targets for the main

Exhibit 10. Feature Distribution For The Second Selection

First Subgroup – Delayed	Second Subgroup – Non delayed
66 % micro-sized companies	75 % micro-sized companies
34 % small-sized companies	25 % small-sized companies
66 % small molecules	50 % small molecules
34 % large molecules	50 % large molecules

thorough investigation. This sample was derived from the results of the first selection and did not follow the sampling logic commonly used in surveys as explained by Yin (2002).

In this study, a "two-tail" embedded design has been used as defined by Yin (2002). Cases from both extremes of a theoretical condition have been deliberately chosen and five embedded units of analysis have been incorporated within each replicate (for the exact definition of research design variables, please see Yin, 2002, pp. 39–55) namely the interviewee background, the development of projects, the strategic direction and the use of competence, the financial situation, and regulatory barriers. Seven final theoretical case replications (Case A–G) were studied in which two subgroups, each including at least three literal replications, were used. One subgroup represented the delayed and the other the not delayed companies. The subgroups include otherwise similar case companies, all of which having comparable features as can be seen in exhibit 10. One critical criterion used when identifying the seven case companies was that the selected companies must have undergone the transition from preclinical research to first clinical trial within the past five years (2005–2010). They also had to be operating at the time of the data

collection. The aim of the second selection was to include the most representative companies in terms of corporate size and the type of molecules developed. Geographically, two major Life Science regions in Sweden are represented in similar distribution as their respective sizes.

3.3.2 In search for primary data

The main form of primary data collected in this case study is derived from focused interviews (Yin, 2002). A total of ten interviews were performed in which seven interviewees were representatives from each case replicate either in the CEO position (six cases), the vice president position (one case) or in the product development manager position (one case). The remaining three interviewees (interviewee X–Z) acted as external expert commentators, selected for their long experience and current positions in larger drug development companies or incubator companies. Only one encounter was set up for each interview in between March and May, and eight of these were recorded and transcribed. Two interviewees chose not to be taped and thus detailed notes were taken at the time of the interview instead. Nine interviews lasted for approximately one to one and a half hours and were carried out at the offices of each company. One fell short to forty minutes due to the interviewee's time limit. The choice of performing a focused interview was due to the time limit and the access of the interviewees. Interview questions were prepared in advance but an open-ended discussion was allowed in between the predetermined structure to get different points of view and freely expressed motivations, emotions and opinions. All interviewees were guaranteed anonymity and each case description presented in appendix 2 has been approved of. Exhibit 11 shows a compiled schedule of the overall methodology.

3.3.3 The Analysis

The analysis was initially conducted by studying each case separately. The five embedded units of analysis were treated one by one and relevant characteristics recognized based on literature and comments from expert interviewees. Once these were thoroughly investigated and structured, the case companies in each subgroups was compared in order to find similarities and dissimilarities within each subgroup. Finally, the two subgroups were approached simultaneously and conclusions were drawn based on the identified characteristics. This kind of "playing with data" is similar to the analytic manipulations summarized by Yin (2002, page 110) and originally described by Miles and Huberman (1994). The analysis is presented in chapter 5.

3.4 Implications of the Statistics and the Research Design

I consider the risk of sampling errors and sampling-related errors, as defined by Bryman and Bell (2005), to be low in this study after the first selection. There is though the potential source of error in the inaccuracy of survey response. Due to some inconsistencies in between each data collection over the years, some statistical insignificance might have been inherited. In this study, I choose to set the statistical significance level to $p < 0.05$, indicating the acceptance of five out of a hundred samples to show a correlation not generally representative, which is still a relatively high significance level (Bryman et al., 2005).

According to Yin (2002), there are four tests commonly used in order to determine the quality of a case study namely the construct validity, internal validity, external validity, and the reliability. Applied here, multiple sources of evidence and the use of key informants reviewing the draft case study report help strengthening the construct validity. The internal validity is by Yin described as being able to establish a causal relationship in the analysis, which is considered to apply for this report. Due to the time frame available, this study is conducted as a pre-study and should be replicated in order to achieve a database with stronger external validity. Although using seven replicates, the results indicate that further studies are necessary if one wish to draw generalized conclusions about all smaller pharmaceutical and biotechnology companies in Sweden. Finally, the reliability is considered relatively high. The use of the database provided by SwedenBIO and the consistent approach of the research should indicate that the operations of the study could be repeated with the same results.

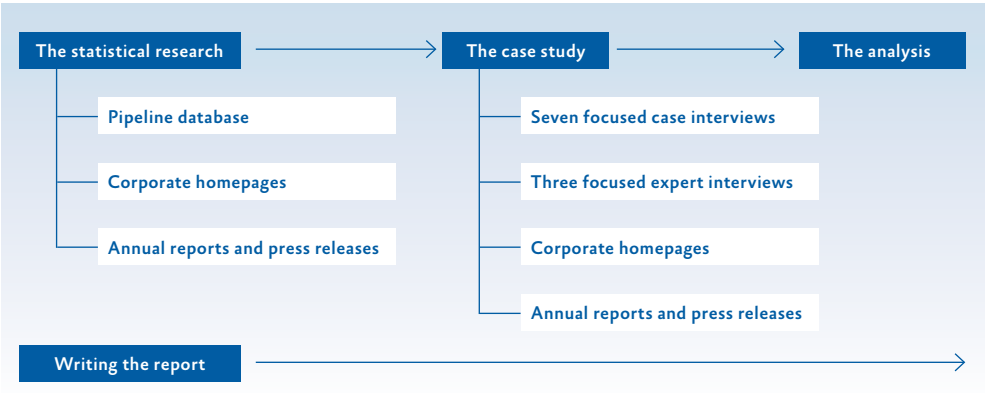

Exhibit 11. The overall method design from statistical research to the finalization of the report.

4 The wakeup call

As mentioned in the methodology chapter, an introductory statistical investigation was performed in order to accurately define the issues addressed in this study. Further on, case interviews were conducted, transcribed, summoned, and briefly presented in this chapter.

4.1 Statistics

When analyzing the database after the first selection, 42 companies and 143 projects remained. The resulting data indicates that the number of projects in the Swedish pipeline has risen since 2006 and 40 % of the drug candidates previously in the late preclinical phase has either progressed into clinical trials or been liquidated (exhibit 12). The concern lies within the remaining 60 % that still lingers in early development. Since the definition in the pipeline survey for late preclinical phase is that a clinical trial will be initiated within a year, these projects should accordingly have moved on in the statistics. This is not the case however and exhibit 13 and 14 shows the number of years spent in each phase for all projects. 30 % is delayed even more than two years suggesting an efficiency problem in the development of these drug candidate projects. It is important to note though that the state in which each project is to be found does not necessarily indicate that they are active in their current development. Many projects are on hold due to lack of resources or as a strategic decision. I consider it to be reasonable to assume that the projects that have been in late preclinical phase for more than five years (~10 %) are dormant projects. They might have progressed as far as the entering of clinical trials before being left on hold and thus cannot indisputably be included amongst the delayed projects. In order to understand what generates these results, the characteristics of the seven case replicates will be presented in the following subchapter.

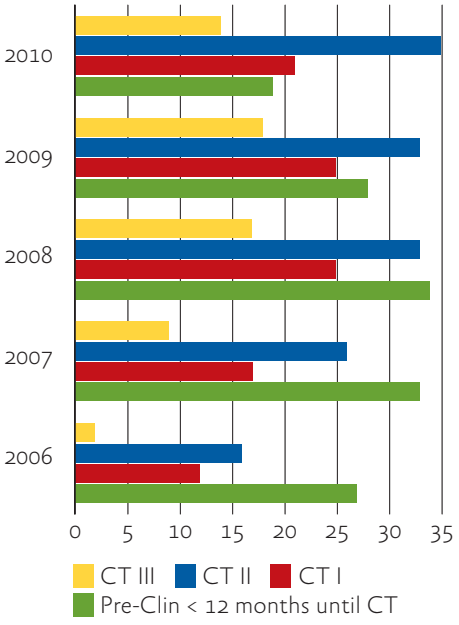

Exhibit 12. The number of projects in each development phase for the past five subsequent years. Source: The Swedish Drug Development Pipeline Report, corporate homepages, annual reports and press releases. Pre-clin: < one year to the entry of clinical trials, CT I: Phase I clinical trial, CT II: Phase II clinical trial, CT III: Phase III.

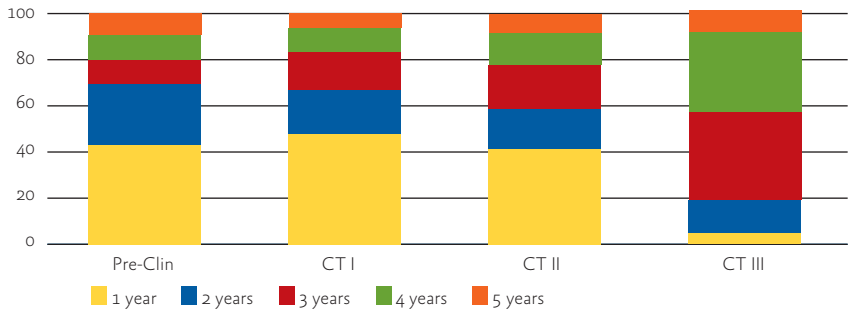

Exhibit 13. The number of projects spending one to five subsequent years in the same phase of development. Shown in percentage. It can be observed that almost 60 % of the projects in the late preclinical phase (Pre-Clin) has been there for more than one year. CT I: Phase I clinical trial, CT II: Phase II clinical trial, CT III: Phase III clinical trial.

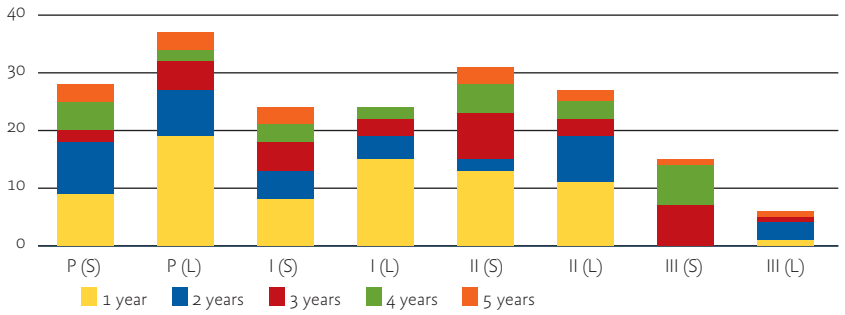

Exhibit 14. The number of projects spending one to five subsequent years in the same phase of development (shown in percentage) when categorized by the type of molecule developed. CT I: Phase I clinical trial, CT II: Phase II clinical trial, CT III: Phase III clinical trial. A total number of 85 small molecules and 58 large molecules are included in the statistics.

4.2 Case Characteristics

In order to simplify the analysis, general characteristics of the cases in both subgroups were identified and summarized as presented in the following sub-chapter. For more detailed accounts of each case used in the analysis, please see appendix 2.

4.2.1 Characteristics of delayed case projects

The three case companies experiencing a delay in the drug development process between preclinical research and clinical trials has been deliberately selected to include the development of small and large molecules as well as representing both micro- and small-sized companies. They are young startups originating from the academia in three different cities and do not yet have any human drug product out on the market.

The development and the strategy

The drug substances in each case company have been derived from in-house research activities in two cases and partly through acquisition in one. Reaching proof of concept is the basic idea stated by all three managers and if possible continued development through out-licensing or acquisitions. They also agree that bringing a first product to the market is of upmost importance since being able to show success increases the credibility of the company making it easier to find investors and partners. Therefore, a development focus has been put in all three cases on one main project with the other ones on hold.

Competence

When it comes to in-house competence, the interviewees expressed different concerns and strategies. They all agree that knowing and understanding the drug development process is crucial, but it has to be to a reasonable price. Hence, two case companies choose to "learn by doing" and recruit new in-house competence only when it becomes financially favorable. The third case company however has partly due to bad experiences with contract organizations and consultants increased its in-house employment ten fold since its establishment in Sweden in order to internally deal with the challenges.

Finance

Financially, all three cases have endured hard times but at least one of the companies no longer needs to worry too much about it. Two of the projects are now funded by venture capitalists and one by angel investors, licensing deals and alternative business operations. Differences have been identified between the two venture capitalist owned companies as well, due to different incentives and desired exit strategies.

Regulatory difficulties

Regulatory barriers were not seen as more difficult to handle than any other activity in the development process.

Delays

The delays in the each case were due to different difficulties in which technical and financial issues, manufacturing issues, and contract issues were mentioned amongst others. But one factor brought up by all interviewees in this subgroup was the occurrence of obstacles not predicted by the people involved. The interviewees did not agree on the order of priority when it comes to the most important factors affecting early drug development (preclinical to clinical) in micro- and small-sized pharmaceutical and biotechnology companies. Instead, they named financing, the technical aspect of the innovation and competence separately as the most important environmental variable.

4.2.2 Characteristics of non delayed case projects

As with the cases in the first subgroup, the second subgroup was also selected to include the development of small and large molecules as well as representing both micro- and small-sized companies. They are likewise academia startups with no drug product yet commercialized on the market.

The development and the strategy

The drug substances in all four case companies have been derived from inhouse research. Once a project has reached the preparation phase for its clinical trial, the companies has chosen to put the rest of its operations on hold in order to concentrate on the more effortful transition. Reaching proof of concept is the common exit strategy for all companies, but whether the exit is intended as an out-licensing deal or as an acquisition differs. They all state that it depends on what opportunities are available when the timing arrives.

Competence

Having a competent CEO, experienced employees, and understanding owners has been stated as an important key to success in all four companies. Although mentioning the importance of benefitting from professional consultants and contract organizations, they also emphasize the need for in-house knowhow. Despite this recognition, the four case companies still choose to stay small since it guarantees financial profitability and chooses only to employ when effectively, but not necessarily efficiently necessary.

Finance

All four case companies in this subgroup are owned by two or three venture capitalist organizations. Two claim not to have suffered any financial complications thanks to supportive owners and good communication. The other two are looking for new additional ways to fund their operations by seeking new venture capitalists or licensing deals for further development. But despite seeing the economical ups and downs as being a natural part of drug development, they both acknowledge the influence of other factors and do not consider their financial condition as that big of a threat to their projects.

Regulatory difficulties

Regulatory barriers were in none of the cases named as the most difficult barrier to handle in the development. Instead, it was considered part of the unassailable process.

Delays

The reasons given by the interviewees as to why these four companies have not encountered any delays in the transition between preclinical research and clinical trials are many. But one factor is the same, namely the in-house competence. They all agree that predictable delays may be prevented if there is prior knowledge of how the drug development process is proceeded and what elements is necessary along the way. As to what environmental factor they found the most important in the early drug development (preclinical to clinical) in micro- and small-sized pharmaceutical and biotechnology companies, two interviewees named the technical properties of the innovation and two named competence.

5 The challenge

Efficiency is achieved in a system when it produces maximum output for the minimum input of resources, as defined by the Gale Encyclopedia of U.S. Economic History (1999) – a state that many companies strives for, but fails to attain. It becomes even more relevant for an operation to be efficient if the resources available are limited. As a consequence of the previous financial crisis, many industries have watched their assets being stripped down and the drug industry is no exception. Despite predictions of better times to come, there are no doubts that we are in for a long, and for some, struggling road to run. For a company to remain profitable and productive at times like these, having an efficient operation is indispensable. In the drug industry, financial difficulties have brought forward other challenges as well, such as the lack of new blockbuster drugs, unsustainable business models, and increased regulatory barriers. These are issues that most professionals in the industry have been familiar with for a long time, but their severity and the implications that follow from them have never been more palpable. The Swedish drug industry is facing the same challenges as the rest of the world and the companies in this country also need to be efficient in order to ensure competitiveness. But, as indicated in earlier chapters, most companies are being too optimistic in their scheduling and rarely progress according to plan. One bottleneck that has been shown to be one of the most difficult transitions to handle in the drug development process is the gap between preclinical studies and the first trials in humans. A number of different accounts are available to explain the situation but there are some common rationales. The following analysis discuss the environmental forces influencing Swedish micro and small-sized pharmaceutical and biotechnology companies and is based on seven case replicates and three expert interviews. How, and to what extent, do the environment affect the efficiency of the transition from preclinical trials to CT I in each specific company?

There are plenty of ways to increase the efficiency within a company but the first step is always the same. In order to do whatever is necessary, we need to identify what needs to be done. When mentioning the delay in the preclinical and clinical transition, no interviewee was surprised. The trend was seen as reasonable and they all agreed that this is no exceptional situation for any micro- or small-sized pharmaceutical or biotechnology company. As can be seen from the recollection of each case, there are plenty of reasons as to why a delay might occur in the gap between preclinical phase and clinical trials. It could be due to unexpected side effects identified through safety tests, substance and manufacturing issues, funding difficulties, the need for extra documentation et cetera. Some of these explanations could

perhaps have been prevented while others could not. Based on these findings, all interviewees tell different stories and thus leave no consistent, concrete reason, as to why this delay continues to occur. Despite the lack of coherency in the recitals, one common rationale could still be identified in all cases, namely the importance of knowing what is to come. If one does not know in advance what to do in order to achieve a certain goal, how does one reach it? Also, if one does not know in advance what might go wrong, how does one prevent it? Hence, efficiency in this case comes with the knowledge of what to do and when to do it so that a plan as thorough and accurate as possible is laid out to guide the process.

All four main environmental factors mentioned in the theoretical chapter were confirmed to have significant effect on the daily operations of all companies, but to a varying extent. Regulatory issues were considered to be the least notable barrier and are thus not discussed separately in this analysis. Competence and innovation were the two forces considered the most influential and difficult by the interviewees, closely followed by financing. This will be further discussed in the following subchapters.

5.1 If I Were a Rich Man

It is clear that the financial crisis has hit the drug industry hard and fast. But despite the constant discussions of lacking capital and funding issues, only one case company named money as the most important and most difficult factor when it comes to drug development. Although other interviewees agreed that funding is without a doubt essential to the business, they all considered other factors at least equally crucial. Since most micro and small-sized companies are supported by venture capitalists that offer milestone payment, the investments are intimately related to the performance and efficiency of company activities. Each milestone indicates the promise of reaching a certain phase within a certain timeframe and in order to ensure credibility, it is best to fulfill them. Accordingly, the operational success and sustainability of a company influence the chance to receive additional funding, which again demonstrates the importance of strategy, planning and competence. Obviously, there is a paradox in the situation since many cases exemplifies how financing is necessary in order to keep a project advancing, and at the same time, progression is what is required in order to get funding. Thus it becomes even more imperative for a company to be as efficient as possible and make the most of what resources are available. As emphasized by interviewee X: *"Not every project is meant to survive. What is desired is that the ones that ought to, do."*

Most companies agree that more funding would not necessarily relate to a change of business strategy. Neither did it necessarily indicate that more people would be employed in order to gain additional internal competence, nor that more projects would be run collaterally in order to lower risks; a faster or more expensive approach wouldn't necessarily be used in order to speed up the process. Hence, additional funding would not induce a faster transition between preclinical phase and clinical trials except for the cases in which finance is the only existing barrier. It should also be added here as elaborated by interviewee X: *"You might be able to overcome the first assessment [the transition from P to CT I] owing only to financial capabilities and luck. But having money and no brains won't take you much further."*

A third aspect when it comes to financing is the funding structure of conventional micro- and small-sized pharmaceutical and biotechnology companies. As most of the professionals in the industry is familiar with, venture capitalist enterprises are the most common source of financing available. The biggest investor commonly considers it to be common sense to be involved in the operations of one's portfolio projects and have the final say about its activities. This structure leads to a special kind of relationship between the owners and the employees that affects the way in which funding is allocated. As argued by the CEO of Company A: *"It is all about working closely with the board in order to ensure their wish to participate in our growth. It is a continuous process and one has to be able to read the signals they give us when they're in doubt."* Once again, the main issue behind funding is about knowledge and communication. If those in charge of a project have the ability to ensure credibility to its owners, funding will to a lesser degree be the reason for a delay in drug development transitions.

5.2 Is Being Innovative Enough?

The drug industry is undoubtedly a research-intensive and high-tech business in which the innovative and technical strength of the product is crucial for the success of a company. But as stressed by the CEO of Company F, it is not only about the quality of the drug but much more about whether or not anyone is willing to buy it. Simply having the best idea and potential doesn't necessarily mean that customers, governmental healthcare systems, or insurance companies are willing to pay. Obviously, an outstanding product will have a better prerequisite to succeed, but as indicated by the CEO of Company E, one will have to be able to show extreme excellence in today's tough climate in order to outshine the rest. When it comes to the transition between the preclinical phase and clinical trials, interviewee Y believes that one might

be able to "cheat" its way through the first gap by having a good strategy and excellent competence, but that sooner or later, the reality will catch up. However, with the majority of the innovations being rarely exceptional, but instead either better or worse, strategy and competence might become "that something" that will differentiate the one from all the others. As also described by Rothwell (1974) and Roberts (1998), having an invention is one thing, but being innovative is another. There are multiple factors involved in successfully commercializing an invention and only taking one into account, in this case the efficiency and safety of the product, is not enough. If the number of strong inventions today may be described by the normal distribution in which only 2.2 % lies in the excellence zone and more than 64.2 % are neither better nor worse. Then the majority of the projects will have to work on the other factors in order to distinguish themselves.

According to E&Y, a number of companies have responded to the financial crisis by focusing on a single "most promising" clinical candidate while putting other clinical projects on hold. But given the serendipity in drug discovery and research it is likely that some innovative discoveries will be curtailed (Ernst & Young, 2009). Not only do the chance of accidentally coming across the next big thing dwindle; it also makes it more difficult for a company to let go of a dubious project. As discussed by four of the interviewees, many projects are bound to fail, that is what the drug development process is all about. So when a company hangs on with one last string of hope to their one and only substance despite its unsustainable character, they are out on thin ice. Based on these arguments, many of the delayed projects that need additional safety studies, effect studies, and other preclinical activities, could be attempts in hopes of saving the company and not true faith in the project. In these cases, when the benefits of the innovation have failed to present themselves, the most industry efficient solution would be to let go.

5.3 To Do Or Not To Do: That is the Question

In all the above contexts, knowledge and competence has come to play a central part of the discussion. To be efficient, better inventions need to be marketed and communicated. Worse inventions need to be strengthened and evaluated, and in some cases liquidated. All these aspects entail people with the knowhow of what to do and when to do it. In this study, it has been shown that the lack of competence within micro- and small-sized companies is the main explanation to the delays in drug development. Especially in the transition from preclinical phase to clinical trial, the first barrier in which the majority is impeded and only the most creditable may pass. According to

all interviewees, there is a major difference between the discovery and the development process in drug development that many fail to concede. *"As a researcher in the academy, there are rarely any strict frameworks or rules to follow. But once you've entered development, you will not only have to keep your toes inside the box, you will also have to document all the frames and regulations you have followed down to the most detailed facts,"* explains interviewee Z. One of the project managers in an incubator company (interviewee Y) agrees, and describes how the appreciation for the business aspect of things is what most young startup companies lacks when they appear with *"the most brilliant innovation of the year"*.

5.3.1 To know what to know makes the difference

Today, most micro- and small-sized pharmaceutical and biotechnology companies are working in a virtual network with only a few full-time employees and a tenfold of consultants. They tend to choose to keep the research knowhow in-house along with a couple of project leaders pulling the strings. The consultants involved in order to manage the daily operations are most often identified through networks and recommendations. This again indicates the importance of knowing the industry when seeking out the right people to rely on. *"If you are not aware of what you need, how will you know who to look for?"* asks interviewee Y. One bad example of what might happen if the competence in-house is insufficient when working with contract organizations is the case of Company G. Their delay in entering clinical trials was to a large extent due to the lack of in-house product development knowledge, leading to the use of an unqualified contract research organization (CRO)[12] as explained by their product development manager. Once they acquired that competence, it took them no more than one year to manage what they hadn't managed in four.

5.3.2 A Swedish perspective?

It is written in the Beyond Borders report 2009 by Ernst & Young, that the conventional wisdom of many smaller Life Science companies has been to "sell their first born" – licensing their initial product candidate to Big Pharma out of necessity in order to sustain operations with the hope of ultimately becoming fully integrated Life Science companies in the future. Amongst the case companies interviewed in this study, none had the intension to mature

12 A contract research organization is a service organization that offers a range of outsourced pharmaceutical and biotechnology research services to aid in the drug development process.

into Big Pharma or Big Biotech, as opposed to the observation made by Ernst & Young. This result could either be due to the inclusion of an exceptional group of case companies in this study. Or, it could be interpreted as a disparity in the Swedish perspective in comparison to the global Ernst & Young perspective. I choose here to believe in the second explanation. Since seven companies with completely different prerequisites are all determined when saying that there is no possibility for a company this size to become fully integrated, it seems difficult to ignore. Despite the long-sightedness of some owners, none has expressed a wish to continue their development single-handedly. As a consequence of the Swedish logic, companies try to keep the costs down in order to attain the biggest increase in corporate value with the least amount of input. One way to do that is to minimize the labor costs. The result is a slower progression of the drug development and delays, as the ones identified in this study. According to interviewee Y: *"It is important to remember that small companies aren't trying to be perfect, they're doing the best they can, which leads to a completely different logic."* Many companies choose to acquire knowledge by doing and thus taking a much longer time than perhaps necessary. There are arguments saying that the lessons learnt the first time around will be used the second time in order to speed things up. But that postulates that the first try is successful enough for a second opportunity to come.
So despite the recognition of the importance of in-house knowledge, most companies still choose to take the risk of putting it all on a few numbers of people. Depending on the circumstances, many may not even experience any difficulties. But the once that do, might because of ignorance, crumble. The balance in the definition of efficiency between productivity and costs has been shifted towards the costs, and productivity has become less prioritized. Despite discussions about venture capitalists rushing for exits as fast as possible, these owners seem to rather take it slow, than invest more in order to speed things up. *"They [the owners] might not be happy about it, but they indulge it. After all, there are no examples of projects progressing faster than expected, only slower."* (Interviewee Z).

5.3.3 Money speaks

Although still crucial, regulatory barriers did not seem to be as difficult and noticeable in the early development discussions as the other factors. Instead, another fourth factor were brought into attention, namely the influence of the owners. As mentioned earlier, most micro- and small-sized pharmaceutical and biotechnology companies have a complex ownership structure with multiple venture capitalist companies involved. These, often industry specific

VCs, are highly active within each portfolio company and has as the main owner the final say in the decision-making hierarchy. Accordingly, understanding and appreciating the drug development process is a must for the representatives from these organizations in order to pertinently support the operations of the company. Also, in academic startups, the board of directors including the owners is commonly the company's first close connection to the industry and hence, their knowledge and support extremely significant for the future development. As mentioned by Barden et al., (2010): *"A good venture capitalist is absolutely invaluable to the success of micropharma and is often more efficient, knowledgeable and responsive than any government funding agency."* But they continue to add: *"However, both sides must remember that this is a partnership of equals. VCs needs scientists just as scientists need venture capitalists."* An understanding that cannot be taken for granted.

5.4 The Final Equation

To sum up, the simplest account of a drug development transition from preclinical phase to clinical trial could in terms of environmental forces be affected by the innovative strengths of the drug candidate, the financial condition of the company, and the knowledge and competence amongst the employees and the board of directors. No matter if you are doing preclinical research in order to prove efficiency and safety in animal models, or ensuring the authority that all regulatory demands have been fulfilled, or attracting investments to finance your project, or if you are planning and setting up the first clinical trial in humans, the three forces will be influencing the outcome of each activity. Through the information gathered in this study, it is clear that competence is the most prominent issue. As mentioned earlier, a good innovation still needs to be improved and developed and a financing opportunity still needs communication and marketing skills. Since most delays in the transition discussed is due to either test failures, omitted documentation, the lack of funding et cetera, knowing and being prepared might be the answer in order to make the process more efficient.

6 Conclusions and discussions

After finalizing all ten interviews, it was apparent that the four environmental forces primarily identified through literature, current debate and other secondary sources were confirmed to be the most influential and difficult to handle in the transition between preclinical research and clinical trials for micro- and small-sized pharmaceutical and biotechnology companies. A strong innovation is necessary in order to show results in the various trials conducted throughout the development process. Funding is crucial in order to perform the operations needed. Also, regulatory demands put all companies on the edge by enforcing rules and legislations to guarantee safety and quality. Despite being the step that involves extensive preparation, early effort, and paperwork, the regulatory barriers were considered to be the least difficult process to handle. Instead, all interviewees agree that it simply is a blockage that one will pass, as long as operations are performed according to framework.

Although all four factors were proven to be more or less important in its own way, one of them has stood out to be of strongest influence in today's environment, namely competence. Based on the analysis, three forms of competence has been derived that to a great extent affect the progression of early drug development (P to CT I):

1. The understanding of what is to come in the development process, being prepared for it, and realizing what ought to be done about it.
2. The marketing and communicating of company and project potential in order to obtain funding and support.
3. The owners and their experience and knowledge that could render valuable networking opportunities and make the collaboration between venture capitalists and the company easier.

If the company lacks any of these three forms of competence, efficiency might not be accessible and the other essential environmental factors such as innovative strength, financial conditions, and the adaptation to regulatory demands might suffer.

6.1 The implications of the Study

6.1.1 Invention versus innovation

Having identified why certain micro- and small-sized pharmaceutical and biotechnology companies are delayed in the transition between preclinical

phase and clinical trials, there are some implications I find interesting to discuss.

Based on the information gathered during the study it became clear that simply having a promising product isn't enough to succeed with the drug development. A fact that has already been argued by Rothwell (1974) and other scholars within the study of innovation theory, although not specifically concerning the drug industry. Who and how one does things matter, not only when it comes to developing the drug substances, but also when in search for additional funding and partnering opportunities. As mentioned earlier, there is a distinction between invention and innovation that is rarely brought up in the context of drug development. As a high tech research intensive field, most discussions on whether a drug substance has future potential or not, refers to the technical aspects of an innovation; an aspect defined as the invention by Schumpeter (1939) when studying the relationship between science/technology and business activities. Schumpeter stated that change in science and technology was interesting only in its ability to transform the outside world and that this transformation capacity had to operate through the mediation of the market place. Obviously, the drug industry with its links to global healthcare and regulatory restrictions is not any ordinary technological product and thus cannot be compared accordingly. But the theory that Schumpeter and then later Rothwell developed contradicted the traditional view of placing basic R&D in front of direct applicable knowledge and should still be taken into account, even in this line of business. As mentioned by some of the interviewees, the potential strength of a drug substance lies as much in its ability to be attractive on the market as its actual effect. Only proving scientific quality and safety does not indicate that a transformation of the market will occur and hence generate value to both the producer and the consumer. Instead, the innovation, as referred to here as the commercialization of an invention including user friendliness, packaging, marketing and other aspects are as well at least equally important to the success.

6.1.2 Tacit knowledge of the drug development process

Financial difficulties in smaller pharmaceutical and biotechnology companies has been a hot topic in debate and discussions all around Sweden, and the lack of funding has been identified as the major issue behind the declining productivity in drug development. This study has indicated otherwise, at least in the earlier stages of drug development. Instead, the lack of competence within companies has been concluded to be a more significant factor in

the failure or success of a project and the communication and mediation of market opportunities more influential. Although this awareness is nothing new to the professionals within the industry, only acknowledging this fact is not entirely enough. It is also necessary to start thinking about the consequences these findings might implicate.

In the theory of knowledge management, a distinction between tacit knowledge and explicit knowledge has been drawn by Michael Polanyi (1966) when classifying the dimensions of human knowledge. Explicit refers to knowledge that is transmittable in formal systematic language, while tacit on the other hand has personal qualities making it hard to formalize and communicate. Also, since all knowledge has its tacit presuppositions, tacit knowledge is not something that can easily be converted into explicit character (Nonaka, 1994). In a drug development company, explicit knowledge can be displayed and conveyed through schemes, plans, reports, consultancy and "instruction manuals" of how the drug development process ought to progress. This category of knowledge is easily achieved trough the virtual network that has become a natural state of learning for the smaller pharmaceutical and biotechnology companies. But when it comes to tacit knowledge, involving individual knowhow based on experiences, crafts and skills, it is not as simple a problem as one would think. This dimension makes available the ability to predict and plan ahead for otherwise unpredictable obstacles, as well as the unexplainable gut feeling of what is appropriate and beneficial in a specific context. Obviously, both dimensions are necessary in an organization that strives to become successful, especially in a knowledge intensive industry such as the drug industry. In order to gain access to tacit knowledge, competent people with experience and knowhow of the entire drug development need to be accessible. In the past, Astra and Pharmacia have been the main source of learning and development, giving its employees the opportunity to gain knowledge of the entire drug development process. These professionals have then used their competency to strengthen the Swedish drug industry as managers of newly founded organizations, board members or owners. Today, fewer and fewer people working within the Life Science sector have that insight, and as the younger generation reaches the managerial positions, the lack of competence that has been proven to be necessary in order to manage and carry out all stages in drug development might become an even more crucial concern for the Swedish drug industry that needs increased attention and at least half the headlines currently occupied by financial affiliations.

6.1.3 The Swedish drug development in a global ecosystem

Another connotation that is worth mentioning is the observation that most case companies in this study lacks the motivation to grow into fully integrated Big Pharma or Big Biotech. In relation to the wavering strength of the Swedish Life Science industry, this cannot be seen as encouraging. "The new ecosystem" as described by Barden and Weaver (2010) is an already well-established and recognized value chain for the new drug industry. The most fundamental part in this "ecosystem" is the relationships between micro, small and big pharmaceutical and biotechnology companies forming a drug development chain that goes beyond the borders of one company. In order to maintain efficiency, a complex network of communication is indispensable and all parts of the system must be available – a prerequisite that the Swedish drug industry fails to fulfill. As mentioned earlier, there is a lack of medium and large pharmaceutical and biotechnology companies in Sweden that should according to the new ecosystem be able to take in the newly discovered innovations emerging from micro and small company clusters. If this cannot be done, the smaller companies will be forced to look for global solutions beyond Swedish soil and the question is: How will that affect the Swedish drug industry climate in the future?

6.2 Further Studies

Since this study is considered to be a pre-study with only seven case replicates, it does not have enough external validly to give definite conclusions that is assumed to apply for the entire Swedish drug industry. Thus, it would be necessary to conduct a more extensive study that covers more cases and observations in order to fulfill the larger objective. The cases included in this thesis are all currently operating companies, and even though some has progressed faster and smoother than others, no real unsuccessful examples have been examined. Therefore, as a suggestion, a more extensive study could include the investigation of liquidated projects in order to compare two truly opposite illustrations. It would also be interesting to have an international perspective to see if the delay is observed in other countries as well. One final suggestion for further studies is to follow up on the case companies included here, in order to see if their views and opinions have changed in a couple of years. Since all of these companies have yet to reach their desired exits, they might have more to learn that could be of interest to the rest of us as well.

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8 Appendix 1 – Interview questions

The following questions were used as a basic structure and further developed to fit each case company and its circumstances before the interviews. Follow-up questions were also prepared in some extent, but room was left for the interviewees' own thoughts and emotions concerning the transition between preclinical research and clinical trials.

1. What is your background and experiences in the drug industry?
2. How and when was the company founded?
3. Key happenings of the company?
4. How has the research and development activities progressed?
5. How many projects have been developed?
6. How many years did each stage take in the drug development?
7. Were there any delays?
8. What is the company's overall strategy?
9. What is the company's core competence?
10. How do you manage the competence level within the company?
11. Do you lack any competence?
12. Does your operational network include consultants?
13. Does your operational network include contract organizations?
14. What is your overall financial strategy?
15. How are you funded?
16. Who are the owners and how do you communicate?
17. Have you suffered any financial difficulties?
    a. If yes, what have been the consequences?
    b. If no, what do you consider to be the reason behind your success?
18. If not restricted by money, would there be any changes in your overall strategy?
19. Do you find the regulatory barriers difficult to handle?
20. How have you managed to find information concerning these?

21. Do you find the need of institutional assistance when it comes to regulatory demands?
22. Which factor (innovation, finance, competence and regulatory barriers) do you consider to be of upmost importance for the failure or success of micro- and small-sized pharmaceutical and biotechnology companies in their early drug development?
23. Do you see any other factors not included as equally important in early drug development?

9 Appendix 2 – Case descriptions

9.1 Case A[13]

A professor at Karolinska Institutet recognized how a Low Molecular Weight Heparin (LMWH) of a certain molecular weight range could ease the complications of protracted labor almost ten years ago leading to the foundation of Company A in 2003. Another twelve professionals from different fields of expertise such as drug development, production, science, and business management joined in to form the company. In the subsequent years to come, different substances stemming from the same molecule but with different molecular weight, targeted towards different indications, were selected and a clinical trial performed. In 2007, the present CEO was recruited to strengthen the market knowledge of the company and in the same year, a second clinical trial was initiated.

Today, Company A has four employees and is located in one of Sweden's largest Life Science clusters. They have also founded a second company working on different candidate substances for other indications in a different therapeutic area.

Discovery and development

The drug candidates selected by Company A are all versions of the same basic molecule, as mentioned above, but with different molecular weights. The three that were chosen to be further developed was identified through the screening of many substances in which these proved to have the best potential of being effective within their separate fields of indication. The selection criteria were mainly based on the results from the *ex vivo* studies conducted. The main candidate drug is now in its second clinical trial and a secondary substance is in its first. Other pipeline compounds are still in early discovery phase.

The progression of the drug development has been rather fast for Company A according to the CEO of the company. After the approval by the Medical Product Agency, it took no more than a year for them to enter Phase I, and another year to enter Phase II. The delays that do have occurred have been due to difficulties in the recruiting of patients in the second clinical trial, an issue solved by opening more clinics.

13 This Case is based on an interview with the CEO of Company A (100412) and company homepage materials.

One of the reasons why things have been progressing considerably smooth for Company A could be due to the well-documented molecule they are working with. According to the CEO, they were not expecting any negative adverse events either in toxicology or in safety: *"Since we already knew that we weren't going to face unexpected obstacles in the process, we were able to work collaterally and hence reach our milestones sooner."* Another factor involved in the successful development of the company is the knowledgeable people working with the projects. *"It's not only about having the answers in beforehand but also about having total control of what's to come in the future in order to be able to prepare for it."* (CEO, Company A).

The organizational and strategic structure of "pharming"

The overall business focus of Company A is to take its projects to proof of concept in humans and then identify an appropriate exit. *"We hope to find a partner that wants to collaborate in moving the project further and in to Phase III. Despite being a small company, we will request strong commitment and geographical reach from a partner,"* commented the CEO. Since the main project has already gotten proof of concept, one part of Company A's work is now focused towards identifying potential partners, either in the field of indication or in the area of the substance. The CEO emphasizes that it is important to be firm and not too submissive in a due diligence[14] just because of the small size of the company. They have also chosen not to profile themselves towards a certain potential partner: *"I don't believe it to be a choice. What if they lose interest? Then it might become even more difficult to find a new partner."* Company A has earlier on been in contact with many stakeholders to market and create an awareness of the company, but the real negotiations have not yet been initiated. *"They [the potential partners] are not hard to find, but they might be difficult to nail down,"* added the CEO.

As mentioned earlier, Company A consists of four employees working full-time with the project, and they do not consider their employment situation an issue. Apart from the CEO, there is one more project leader, one scientist and one responsible for the documentation. There are also twelve core consultants working with the company and another 30 in the outer network. Another source of knowledge mentioned by the CEO is the board: *"The reason as to why we are able to have so many projects running is due to the existing expertise at hand amongst our board members and consultants."* The CEO explains that what it boils down to when considering competence management is

14 Due diligence refers to the investigation or audit of a potential investment.

whether or not it is more efficiently effective to employ someone full-time or to continue to work on a consultancy basis. *"As for now, we are not lacking competence. But we do wish to have another project leader to run and coordinate one of the projects. And when the timing comes, we will recruit that someone,"* adds the CEO.

The core consultants that are involved in Company A have been with them since the beginning. They joined in, as mentioned earlier, during the formation of the company, and these are the ones primarily consulted. The others have gradually been included and have mainly been acknowledged through contacts. When it comes to contract organizations, Company A is working with many from different parts of the world. The evaluation criteria have been more focused on the potential quality of delivery and less on geographical barriers. *"We choose by interpreting their [the contract organization's] commitment and through personal contact. There sure are difficulties with language and culture, but it's not a decisive factor,"* ensures the CEO. Company A has also worked with both larger and smaller contract organizations, all of which have delivered good results. But as the CEO adds, they still believe that in the long run, it is better to collaborate with a company that understands the implications of being small.

The financial situation of the company

Company A is a privately held company with three major owners who have been with them since the foundation of the company. One representative from the biggest owner is part of the board and acts as a link between Company A and the others. According to the CEO, the owners have all been very supportive of their work and thus have not put them in any financially difficult situations. *"It is all about working closely with the board in order to ensure their wish to participate in our growth. It is a continuous process and one has to be able to read the signals they give us when they're in doubt."* (CEO, Company A).

Apart from VC money, the company has applied for different grants, both from Sweden and other countries. Although none received, the CEO still believes it to be worth the time and effort: *"It is a good way to create awareness, so despite the loads of work, we are not giving up."*

The big picture from the CEO of Company A's perspective

When discussing the four main environmental factors recognized in this study to influence the drug development process in a micro- and small-sized pharmaceutical and biotechnology company, the CEO of Company A names strategy and demand as the most important. *"No matter how fantastic the product is, without the demand, it will not be worth it,"* argues the CEO. He also emphasizes the importance of realizing the weaknesses of an idea as early as possible to avoid aiming too high from the beginning, and thus fall flat half way in the process. One other important issue not stated amongst the four major influencing factors is documentation. According to the CEO, a lot of people are not aware of the necessity to document all activities from the beginning. This might cause difficulties and delays once realizing that the required information is not available when needed.

9.2 Case B[15]

Company B was founded in 2001 when a Professor at Karolinska Institutet identified bio-molecules with the ability to affect apoptosis, programmed cell death, a mechanism involved in many diseases. Based on this finding, new bio-molecules were developed that potentially could be used in treating these diseases. By 2007, the owners decided that the project was mature enough to move on from discovery phase to development phase. New personnel were hired to acquire the industrial knowledge and competence needed for drug development. In the past three years, a business model has been put together and the operational process is in progress. Several IP (intellectual property) rights have also been granted, and the main drug candidate prepared for entering the first trials in humans (clinical trial Phase I, CT I).

Today, Company B employs six people, is located in one of Sweden's largest Life Science clusters, and is run by their two key management members – the CEO and the head of pharmacology. The overall business focus is to develop their main drug candidate in one niche indication, from discovery to clinical proof of concept (early Phase II).

Discovery and development

During the years in the discovery phase, Company B identified two branches of bio-molecules as drug candidates, but the development focus has been

15 This Case is based on an interview with the CEO of Company B (100317) and company home-page materials.

put only on one of them. This is, as explained by the CEO, due to the size of the company and its limited resources leading to a need to focus. As for the evaluation criteria, technological strength and market potential were the two foremost important and inseparable reasons behind the choice. Also, the main drug candidate has no disclosed competition making it unique in that sense. There are several potential indications for the compounds since the underlying mechanisms are, as mentioned above, involved in many disease processes. But again, due to limited resources, the development focus has up until now been put only on one niche indication.

The progression of research activities has according to the CEO generally followed the operational plan since 2007 with a few delays, mainly due to technical and financial issues. As explained by the CEO: *"There are always aspects in drug development that takes more time than one intended them to, it's difficult to state out one specific thing as the reason behind it all."*

The organizational and strategic structure of "pharming"

As described above, the overall business focus, since the establishment of the company, is to discover and develop their main drug candidate from discovery to proof of concept. In parallel, they intend to search for opportunities to out-license to a Big Pharma for further clinical development and future market entry. This strategic decision is based on a classic business model for small drug development companies where the value of the company is considered to have increased after proof of concept for reasonable amount of investments, making it a profitable strategy for the owners. But although this is the theoretically supported plan of action, the CEO of Company B still emphasizes the importance of being open to other opportunities.

Company B is presently planning for their main drug candidate to enter CT I with the chosen niche indication. If the trial goes as planned, continued development to reach proof of concept will follow in preparation for the intended out-licensing. The other candidates and indications will then be value-adding components in the evaluation of the company. But if the CT I do not render as optimistic results as anticipated, a backup plan – which consists of an alternative candidate drug (an altered version of the main candidate) – could be developed. Company B has also already initiated discussions with potential investors as they find it important to plan ahead. As explained by the CEO: *"It is important to have an idea of what they want and profile oneself accordingly. You can't showcase the same package to two different companies."*

Since Company B only consists of six employees, it is not possible to have all the relevant knowledge in-house, and due to financial reasons, employing is out of the question. According to the CEO, the solution they find most applicable is to use consultants in different areas. *"One can always use more knowledge in-house, but we can't afford to have money tied up in personnel, hence the consultancy solution."* (CEO, Company B). The consultants involved are very active within the company and act as the initial communication channel between Company B and other specialists such as CMOs (contract manufacturing organizations), CROs (contract research organizations), and regulatory experts and the like – also of great importance to the company. As further explained by the CEO: *"We do what we do best, namely the fundamental biology and protein research in the earlier phases of drug discovery and development. The rest we leave to the people that have their expertise in the specific areas of process development, production, preclinical tests, safety studies and clinical trials."* The company works with different contract organization on different branches of the development process and considers the quality of delivery good in general. *"I'm sure they [CMOs and CROs] have a very good market considering the sometimes limited knowledge out there on what to do and when to do it."* (CEO, Company B). But although the expertise of a contract organization is somewhat assured by the word of mouth between contacts, the CEO points out that in-house knowledge is still necessary to be able to preserve control. *"One can never expect the contract organizations to be as committed to the project as we are, or for them to think outside the box when delivering. They go as far as we tell them to and no more."* (CEO, Company B).

The financial situation of the company

Company B is privately owned and has three shareholder groups, namely the founder and two Swedish venture capital companies (VCs), all of which are represented in the board of directors. The founder is still active as the research adviser of the company; the VCs, both supporting Company B with almost an equal amount of funding, direct the development process along with the chairman of the board. Since the VCs are the main investors, they are facing a lot of risks, as pharmaceutical investments are not the cheapest ones to be involved in. In response, the owners control the project, the milestones and their budgets tightly. *"The ownership structure in most small pharmaceutical companies is complex. Having two almost equal sized VCs is sometimes difficult. But for us, it has been more of an advantage. They both work on a comparatively common ground and generally have consensus in what to do."* (CEO, Company B). Apart from VC funding, Company B has also applied and received

grants from VINNOVA and different EU funds. But as emphasized by the CEO: *"Grants usually doesn't involve that much money, so we have used them earlier on to finance smaller tests and projects. As for now, when approaching the manufacturing and clinical phase, we are in for the bigger cash and thus can't rely on grants to do the job. It's just not worth the effort."* The CEO also argues that there is a gap between preclinical studies and clinical trials when it comes to funding. In order to perform the costly first clinical tests, investors are crucial. But in order to find investors, the results from clinical trials are necessary. One of the reasons why it might be even more difficult for Company B to find funding is the additional costs related to the production of large molecules instead of small molecules – *"a cost often forgotten,"* reminded the CEO. It was never disclosed how far in the future Company B's current financing covers their operating expenses. The CEO did reveal though that their project needs funding for another three years before the intended exit.

The big picture from the CEO of Company B's perspective

When discussing the four main environmental factors recognized in this study to influence the drug development process in a micro- and small-sized pharmaceutical and biotechnology company, the CEO of Company B names financing as the most important. But not far behind is product strategy and business development knowledge placed as the second most important factor for a successful business. As elaborated by the CEO: *"I don't believe most people are considering the nature of their end-product in beforehand. Maybe they get stuck for too long in the preclinical discovery stage instead of moving on to the development stage, also not realizing the big difference between those two."*

9.3 Case C[16]

Company C started up as a classic academic spinout year 2000. One professor at Karolinska Institutet had a specific idea that a certain substance should behave in a certain way in inflammation diseases. An idea that resulted in the first set up of a clinical trial in humans the same year. After achieving very positive results, a second clinical trial was prepared in collaboration with an international Big Pharma. The only requirement on Company C was to conduct a larger trial than first intended, i.e. doubling the number of patients. In return, Company C received a significant milestone fee for future licensing rights. In 2004, the results from the second clinical trial were made

16 The case is based on an interview with the Vice President of Company C (100318) and company homepage materials.

available and ended in disappointing conclusions. After examining the possible cause for these results, Company C realized that due to their lack of certain aspects of preclinical knowledge, the trial was conducted differently (the patient population were somewhat different) when compared to the first trial, and hence the setback. It took Company C another two years to fully grasp the underlying mechanisms of their compound, during which the rights to develop and commercialize the main candidate drug once out-licensed was returned by the Big Pharma. With a better understanding of all the mechanisms involved in their compound, Company C conducted a third clinical trial (Phase II). This time, although with fewer patients, but with the same category as in the first clinical trial, the positive results anticipated were achieved in mid 2009.

Today, Company C employs twelve people and is located in one of Sweden's biggest Life Science clusters. They also have, together with its pharmaceutical operations, a fully owned subsidiary working with diagnostic products.

Discovery and development

Company C's pipeline consists today of different immunomodulatory candidate drugs. The main candidate drug has, as mentioned above, recently been through its third clinical trial for one of its several potential indications. Only a limited amount of resources have been invested into the other pipeline candidates this recent year. As explained by the Vice President, VP, of Company C: *"The main focus is now being put on progressing and ensuring the advance of the main drug candidate. It is always easier once you've gotten a success story to tell."* The VP also mentions how the clinical trials often claim substantial attention of a company the size of Company C, and thus when having one project there, the rest will automatically have to step back for a while. *"It is of course also a question of money,"* continues the VP.

Since Company C managed to start the first clinical trial back in year 2000 without extensive preclinical research; their advance in the development process has been rather fast. *"For us, the opportunities really has been presenting themselves one step ahead of us,"* the VP pointed out, *"and when you put that into the drug development model, we have almost progressed too fast. Especially the clinical stages, and thus leaving the surrounding activities such as toxicology and formulations somewhat behind."* Company C did not have any delays between the preclinical and the clinical stage of drug development. Instead, they had to speed up and redo some of the earlier steps later on leading to delays in the

project development phase. But the VP also points out how they, by obtaining their first clinical trial results that early in the company's history, gained a major advantage that made it easier to find licensing partners and financiers early on.

The organizational and strategic structure of "pharming"

Company C is presently working along two major routes to find a solution that will ensure the progression of their main project. Throughout the development process, there have been several underlying strategic targets but no fixed business plan as to how, when and what to do. In the beginning it was all about identifying the right intellectual patent combinations to cover all substances in the company pipeline. Then it was about getting enough data to use when looking for ways to commercialize the project. Right now, Company C is evaluating their choice to find a licensing partner for a comprehensive Phase III study on their main candidate drug and/or to find additional venture capital investments to enable a pivotal Phase III trial on a more specialized indication with the ambition that it will be enough for registration. As explained by the VP: *"We don't have a coherent strategy because it is not possible – that, we know from experience. We have two alternative ways to proceed and are working with both of them."* Working both ways, the company has initiated collaborations with some inflammatory bowel disease specialists in a European country to start testing its product on patients in a specific indication under a so-called compassionate use program. The company has also initiated discussions with several potential future licensing partners. To create awareness of the company portfolio, they have chosen to work with an external representative that will travel the world displaying Company C's case and attract attention on different partnering events. *"The challenge is to be seen amongst all those thousands both good and worthless innovations,"* commented the VP.

The size of the company is, as stated by the VP, always an issue in smaller companies. Company C normally has twelve employees but they are right now down to ten. Amongst the employees, the CEO has, on top of his medical education, a strong background from the financial/investment sector. A few have experience from the Big Pharma industry. But the majority comes from an academic background. *"In a way, I would say that we for sure lack internal competence in several areas relevant when it comes to developing new medicines,"* explains the VP, *"so it's down to having a number of consultants that can help us."* Company C is engaged with approximately ten consultants in their everyday operations. These consultants are commonly identified through namedrop-

ping within the company networks, and one hopes to find the experts within each relevant field. *"There are plenty of consultants out there, but whether there are enough good ones or not, that's a different question,"* (VP, Company C). Company C is also using contract organizations for different stages of the development process, but finds it difficult as a small company to identify the ones offering the best support. *"Will they deliver a good enough product and do they really have the competence they claim? Also, will they treat your project as if it was their own? To be able to figure these questions out, you'll need a lot of in-house competence."* (VP, Company C).

The financial situation of the company

Company C is currently privately owned by a total of 101 shareholders. The dominating part of company financing has come from venture capitalist investments and milestone payment from license partners. The two major shareowners are represented within the board of directors as members, and they have been very interested in the activities of the company, following its progression closely. There has also been a third large VC financier, but they left a few years back. According to the VP, no research grants have been applied for: *"I understand us to be too big to be able to find cash large enough to make a difference,"* commented the VP, *"ok if a scientist gets half a million for a project, but our basic turnaround is 25 million a year."* Another reason for not applying is the connection the VP sees between grants and certain future conditions and requirements. *"The VC money is not conditional in the same way."* (VP, Company C).

Having been through seven financial rounds, the monetary condition for Company C has been going up and down through their ten years of operation with some years being more difficult than others. The past years financial crisis has also left its mark on the progression of the company. *"There's a cycle out there affecting us all when it comes to finance. The past years have according to everyone been pitch-black, and we wouldn't have made it if our major owners hadn't temporarily backed us up again."* (VP, Company C). Company C has also earlier worked for the possibility of entering the stock market but had to withdraw due to the unexpected results from the earlier second clinical trial. Now, the discussion has been lifted once again, but according to the VP, it will not be of real interest until the plans for the future operations have been set. The current economic situation of the company will not cover its activities for long. But even though the future is unclear, the VP is optimistic: *"We are working on two solutions to our financial situation and I am unmistakably positive. I think we can do it."*

The big picture from the Vice President of Company C's perspective

When discussing the four main environmental factors recognized in this study to influence the drug development process in a micro- and small-sized pharmaceutical and biotechnology company, the VP of Company C names the technical part as the most important. Although financing is always needed, the technology is still considered more essential. The VP also states that the regulatory difficulties are not a very big issue since there are certain rules and guidelines to follow, and all companies have to get through them.

9.4 Case D[17]

Company D was founded in 1998 by two professors at Lund University after the identification of a biomarker for cartilage turnover. They spent most of the first two years developing diagnostic products when discovering their first drug candidate in year 2000. Working both ways, the company struggled to finance its operations until the present day majority owner got involved in 2003. One year later, the current CEO joined Company D with the intention to strengthen their pharmaceutical sector, leading to the acquisition of four new candidate drugs.

Today, Company D employs thirteen people and is situated in one of Sweden's largest Life Science centers. The strategic orientation of the company is chronic joint diseases with a pipeline consisting of five drug substances, one currently finishing its first clinical trial.

Discovery and development

The discovery and development process of Company D differs slightly from the typical academic startup model with the acquisition of its four substances. These drug candidates originated from the chemical library of a research and development/consulting company where they had, at the time of the acquisition, already progressed past basic research. According to the CEO of Company D, the earlier relationship between these two companies lowered the barriers of entry and thus facilitated the acquisition.

The progression of Company D's research activities has had a distinct delay due to a substance quality issue. It took the company up to one year to resolve the setback, leading to the postponement of other related activities. Apart

17 This Case is based on an interview with the CEO of Company D (100414) and company homepage materials.

from this major misfortune, there were also other happenings taking up time. Facing earlier unmet difficulties, the CEO believes it to be inevitable for most newly established companies to find themselves somewhat behind schedule: *"When being such a young company as we are, every task we perform beyond preclinical research is our first. Consequently, things are going to take more time than perhaps necessary. It is definitely a tough learning process."* Having been aware of these circumstances in advance, Company D has chosen to explicitly express the need to proceed with a broader range of projects in a slower pace and more accurately. *"We are aware that we could have speeded things up from the beginning, but that would have been to a completely different cost and at a different level of risk, so we chose to do the opposite,"* adds the CEO. Once they achieved enough data, the substance with the earliest best preclinical results was chosen to be the main project. With one running full speed in its clinical trial, the other projects are forced to a slower progression. The pharmaceutical pipeline of Company D also includes two substances not completely in line with the strategic core of the company and thus has been put on the market for out-licensing opportunities.

Despite already being involved with five pharmaceutical pipeline projects, Company D is not opposed to bringing new ideas onboard either through internal research or external sources. They are constantly on the lookout for new possibilities, although not actively at the moment. *"If we find something more promising than what we've already got, we would probably be interested in switching our focus,"* states the CEO.

The organizational and strategic structure of "pharming"

Three years ago, Company D's business strategy was distinctly altered when they realized that their first objective, not to take any project further than preclinical research, was proved to be inapt. After recognizing the change in customer preferences, the company adapted itself to the new market conditions and took its projects further down the drug development path. *"It was a tough challenge but everything depends on the current situation,"* explains the CEO. The company has also initiated the search for future potential partners but is convinced that trial results say more than words. They therefore choose to gather as much data as possible before showcasing their offer.

The core competence of Company D is in the hands of thirteen employees including the CEO, the IP manager, ten scientists and one responsible for the economy. Being a small company, they have to make the best of whatever resources are available. *"Some of our scientists are now building some basic regu-*

latory and clinical competence to become somewhat conversant in these respective areas," mentioned the CEO, *"we learn by doing."* Since Company D wants to avoid the accumulation of fixed costs, they see the use of consultants as the best solution. New recruitments are only carried out when the demand reaches a critical mass making the consultancy solution no longer appropriate: *"It isn't about trying to use up all the money we've got, it's about using them when necessary. We will not hire just to increase our physical size, we will hire only when it is the most cost effective thing to do."* According to the CEO, research is what Company D does best and thus is kept in-house. Another source of knowledge not to be forgotten is the contribution of the board. The consultants and contract organizations that are involved in Company D's operations are mainly recognized through their skills and brand recognition. Geographical location has not been an issue. The company has chosen to mainly work with the international big brands since the CEO "imagine" it to be an advantage to have been working with the contract organizations that are well recognized amongst Big Pharma. The delivery has been considered satisfactory so far.

The financial situation of the company

Company D is a privately held company mainly owned (70 %) by one major holding company since 2003. Before that, the founders spent most of their time, trying to fund the next month's activities through different loans and smaller investments. After the holding company got involved, Company D has not experienced any more financial difficulties and the CEO have been able to put all efforts into project operations. According to the CEO, Company D has not applied for any grants apart from a EU initiative currently running. *"We do have mixed feelings about our involvement. On the positive side, we gain financial support and some new contacts, but the bureaucracy scares us,"* explains the CEO, *"if it wasn't for our collaboration with the University in charge of the project, we wouldn't have participated."*

The owners of Company D has a long-term interest in the company with the objectives to build an independent organization, making it possible for the company to work in its own pace. There are no intensions to become public and the CEO does not see it as a viable option for anyone. The only possible outcome according to the CEO is involuntary shortsightedness.

The big picture from the CEO of Company D's perspective

When discussing the four main environmental factors recognized in this study to influence the drug development process in a micro- and small-sized pharmaceutical and biotechnology company, the CEO of Company D names the technical product as the most important. But not far behind is marketing abilities and strategic awareness placed as the second most important factor for a successful business. *"I assume that the ability to market oneself is always an advantage, but I hope it isn't too advantageous,"* says the CEO. Another factor brought forward is the contribution made by the board of directors. The CEO argues that the ownership structure in many smaller pharmaceutical companies is very complex, and that the directors representing the venture capitalist companies involved are commonly fixated on protecting their own benefits in this matrix instead of on what's actually best for the company. *"I'm certainly aware of our luck of having an owner that is in it for the long run. It makes such a difference!"* (CEO, Company D).

9.5 Case E[18]

Company E is a small pharmaceutical company with one candidate drug in its first clinical trial, primarily focused on hematologic diseases. It was founded in 2003 in order to be able to enter the 6th Framework Programme (a funding programme set up by the European Union in order to fund and promote European research and technological development). The molecule was found during research activities at Karolinska Institutet by a team consisting of one professor, three docents, and two PhDs. During its first operating years, only one or two people worked part-time in the company. Later, in 2006, the number of personnel increased slightly. But it wasn't until 2008, when the current CEO was recruited, that the size of the company reached today's total of six employees.

Company E is now situated in one of Sweden's largest Life Science clusters and the progression of the development process has gone from basic preclinical studies, through toxicology and IP programs, to CT I and commercialization. Further plans for 2010 is to implement the strategy for CT II and outline future modes of action.

18 This Case is based on an interview with the CEO of Company E (100329) and company homepage materials.

Discovery and development

The candidate drug presently in clinic is the one developed the furthest by Company E. Additional backup compounds, running at half-speed, is as well present in this project for better compliance. The company's pipeline also includes two completely separate programs, which are still in early discovery phase and currently on standby due to financial reasons. Company E's evaluation criterion to focus only on its main candidate is the level of value exchanged by the main project. As explained by the CEO: *"Good results here [in the main project] will grow more value to the company than any effort put into the others [the secondary projects] will at the moment."* Apart from value adding, the market situation is also beneficial for the main candidate drug since no one has been able to do what Company E is doing so far. But the CEO adds that if it was up to him, he would have preferred to have more projects up and running to reduce the risks involved of being a "one idea-business".

The progression of research activities has according to the CEO been as planned for the past two years, with the exception of some delays in the clinical trial recruiting process, which was solved by opening more clinics. However, there were drawn-out processes in the preclinical stages before his time, mainly due to the lack of knowledge on how to move the project from basic research to product development. Other sticky factors might have included filing applications and supplements or being overly optimistic when scheduling. As explained by the CEO: *"Before entering product development, the preclinical phase is pretty straightforward. But once you start wrapping these into a package along with development and manufacturing, it gets complicated. I don't believe a lot of projects have that knowhow."*

The organizational and strategic structure of "pharming"

The business strategy of Company E is to gather as much data as necessary to enable a sale that ensures payout to the owners. Other possible exits might be to out-license or engage in partnership deals. *"I believe that the earlier intension were for Company E to sell the project already after its first trial, but I doubt it will be possible. The kinds of [risk-reducing] data that will attract Big Pharma's interest in those stages are rare today considering the high set standards."* (CEO, Company E). Furthermore, the CEO affirms that the owners have no plans to expand the company; it is believed to be difficult since the facilities of a "one idea-business" are not favorable for long-term growth.

As mentioned earlier, Company E has today an employment of six people, most of which are recruited after the arrival of the company's current CEO.

"One thing that I have learnt from earlier experience is the necessity of having the right competence. Nobody can have all the knowhow so you'll need a team of at least six people to do the job." Apart from the full-time employees, Company E uses a group of 10–15 consultants to deal with the issues not manageable within the company, most of whom the CEO have had past working experiences with. When working with an internal group of people as well as an external group of consultants, the CEO emphasizes the importance of having a plan and knowing in advance what to be expecting. *"If you don't know what situations awaits you in the future, then you will not know what knowledge you'll need in order to deal with them."* (CEO, Company E). Company E has chosen to keep the project leaders and the preclinical scientists in-house since these are the core competencies though to be most valuable internally. The CEO of Company E also mentions how it would have been in their interest to recruit another two or three project leaders since it is not desirable for one to be working with too many consultants. But due to financial reasons, this is not yet possible.

Apart from consultants, Company E involves different contract organizations in different parts of the process. The choice of an East Asian-collaboration was before the present CEO's time but he assumes that the competitive prices were the primary attraction. *"They have delivered decent results so far, but there are definitely [geographically] closer contract organizations that are able to do the same quality job with less administrative and social complications,"* explains the CEO. When it comes to the other organizations, located primarily in Sweden, earlier recognition through networks has been the major reason behind the choices.

Company E is now in the process of drawing awareness to the company in preparation for the future exit. They will also, after the results from the first clinical trial, try to find potential partners that might be interested in getting involved before the second trial. *"It often takes about 6–12 months to sign a deal, so it's worth starting preparation early,"* states the CEO.

The financial situation of the company

Company E is privately owned and has four major shareholders financing their operations. Two of these are represented within the board as well as two of the cofounders. Other board members are experts in different fields of relevance. The current financial support covers all company activities within this year, but no more. The original expectations were to find a partner in order to support the first clinical trial but that opportunity has not yet

emerged. Instead, an alternative plan is now executed in which the company has involved a VC expert in search for two new owners to support its continued development. *"The competition is tuff. It's not like there are plenty of venture capitalist companies out there scanning only Swedish Cancer projects. But since we've come quite far in our development, it will hopefully increase our chances,"* said the CEO.

Apart from venture capitalist investments, Company E has applied for and received Swedish grants to finance its operations. They have also, up until recently, been supported by the 6th Framework Program as mentioned earlier. But the CEO states that they will spend no more time applying for different grants: *"It's too complicated. Some are ok, but the EU grants are too extensive. The time required to apply and wait for the decision is much better off spent in search for new owners."*

The big picture from the CEO of Company E's perspective

When discussing the four main environmental factors recognized in this study to influence the drug development process in a micro- and small-sized pharmaceutical and biotechnology company, the CEO of Company E names competence as the most important. Although emphasizing that all four factors are crucial in its own way for a successful development, the CEO argues that there is a possibility that a mediocre innovation could render better potential with the right competence at hand than a brilliant innovation could if handled less skillfully. According to the CEO, many smaller companies are very reliant on their board of directors and hence need experienced and knowledgeable members. Since the investors are commonly represented within the board, their understanding of the drug development process is as well crucial to the company's decision-making process.

The second most important factor from the CEO's perspective is the innovative and technical strength of the project. Both financing and the regulatory activities are seen as achievable as long as the first two requirements are met. Other important factors not mentioned are leadership and communication: *"One has to be able to engage and motivate others in doing what they do best. Also, endurance and patience are aspects worth mentioning."* (CEO, Company E).

9.6 Case F[19]

Company F was founded in 2006 as a subsidiary to the organizational group led by a leading professor after his discovery of a new way of treatment that is likely to be applicable in a various range of indications. The focus of Company F has been put on one of these disease areas whilst a second subsidiary is profiled to one of the other plausible indications. The parent company was established in year 2000 and although both subsidiaries have the same CEO, they are treated as two separate entities due to financial and operational benefits, and thus will be described as such in the following text. Company F is the subsidiary that has progressed the furthest with its lead drug candidate in the planning stage for its second clinical trial.

Today, the company is located in one of Sweden's largest Life Science clusters with only the CEO as a fulltime employee. The overall business concept is to demonstrate new opportunities within the field of CNS or Women's Health in the search for a future potential partner or a merger & acquisition (M&A) transaction.

Discovery and development

Company F is currently working with a set of substances within their specific field of indication, all of which derived from their internal research facility. Its lead drug candidate has in the past four years progressed through all necessary safety studies, a first clinical trial in humans and is now advancing towards its second clinical trial. It was selected due to the high amount of data available and the benefits it possessed that enabled a sooner entry into clinical development stages. The other substances are seen as value-creating components in the company's strategy, indicating lifecycle management and long-sightedness.

Most of the preclinical studies performed on Company F's lead substance were conducted before the foundation of the company and followed an academic approach, meaning less stringent time schedules and rather inefficient efforts. But once the subsidiaries were formed and the CEO recruited – bringing a stronger knowledge of drug development into the company – things have progressed fairly smoothly. According to the CEO of Company F, there have been no major delays apart from the extended first clinical trial. *"We recently encountered some difficulties concerning the appropriate mode of prepara-*

19 This Case is based on an interview with the CEO of Company F (100319) and company homepage materials.

tion which has led to a postponement of related activities," says the CEO, *"but we are almost through now and soon we'll be entering Phase II."* The CEO continues to explain how: *"certain activities will surely progress slower when doing them for the first time. But the lessons we learn when working with this lead drug candidate will most definitely be used to speed things up for the next round."*

The organizational and strategic structure of "pharming"

As mentioned above, Company F's business strategy is to develop its novel treatment principle until proof of concept is demonstrated, while searching for a strategic partnership or a transaction opportunity. Although the strategy is not "set in stone", the CEO doubts that there will be any changes: *"It all depends on the money, even if that's a bit sad for me as a former academic to admit."* According to the CEO, there are plenty of models indicating how the maximum increase of value is being created in the company for the least amount of resources when progressing from a first clinical trial to proof of concept. Furthermore, since Company F is financed mainly by venture capitalist organizations, the investors are expecting a timely exit in compensation for their continuous support. *"The resources necessary to pull off a Phase III clinical trial is more than most smaller companies can handle. It's not only about the money but organization wise as well,"* claims the CEO.

Company F has already started looking for partners through different networks and partnering events. *"I know very well from past experience that finding a partner and signing a contract takes a long time, so I've decided to start early,"* says the CEO. She is at the moment trying to identify the interested companies and making them aware of Company F's existence and what they are planning to offer. The objective is to increase as much company value as possible and at the same time show transparency. If appropriate, the company might also slightly alter its projects to fit the profile of potential partners. *"I believe it's good to get some feedback on our case from our stakeholders since it makes it easier for us to create a more attractive package,"* adds the CEO.

Having only one fulltime employee, Company F is utmost dependent on consultants and contract organizations to support them in their operations. Some of these are assigned to the company in longer contracts whilst some in shorter. The CEO does not give any specific reason as to why they have chosen not to employ: *"It simply turned out this way and it has worked well so far."* The consultants involved in the company have mainly been acknowledged through networks and recommendations. According to the CEO: *"being situated in the same building as other Life Science companies really makes these kinds of*

things [finding help and recommendations] much easier." Contract organizations are also mainly found through networks. Price is considered important but not as critical as how they treat their clients. The CEO of Company F sees advantages with both larger and smaller contract organizations: *"It is easier to get full attention when collaborating with a smaller CRO, but at the same time, a larger CRO with a stronger brand awareness that Big Pharma is familiar with might benefit us in a due diligence."*

The financial situation of the company

Company F is a private company owned by its parent company and two venture capitalist organizations. In the beginning, only one of these VC companies was involved and the majority of the shares are still in the hands of that company. The second VC joined in later on and the CEO is now considering bringing in a third investor. Despite the recent financial crisis, Company F has not experienced any financial difficulties. The owners are according to the CEO very supportive and very inclined to keep their amount of company shares. *"Sometimes, it's almost as if they [the VCs] are too committed and not willing to give anyone else the opportunity to get involved,"* laughs the CEO. Company F has not applied for any grants to fund their development activities due to the increased workload involved. The parent company though, has applied to some, but only because of their focus on basic research rather than drug development. According to the CEO, excess financial availability would not change how things are handled within the company. *"Our business strategy would stay the same."* (CEO, Company F).

The big picture from the CEO of Company F's perspective

When discussing the four main environmental factors recognized in this study to influence the drug development process in a micro- and small-sized pharmaceutical and biotechnology company, the CEO of Company F names the innovation as the most important. But she also adds that it is not, as often assumed, the future potential of the product that is important. Instead, it is whether or not anyone will be likely to pay for it in the end that counts. Another factor brought up was the importance of being able to explain ones project. *"There are so many stakeholders involved in a drug development process [investors, collaborators, media, potential partners and buyers et cetera] that you have to convince in order to succeed. So if you're not the least pedagogic, that might become a problem,"* elaborates the CEO.

9.7 Case G[20]

Company G was originally founded in a European country outside of Sweden in 1998 by a couple of researchers at a University. Due to some country-specific regulatory difficulties, the entire organization, consisting then of six scientists and the CEO, moved to Sweden in year 2000. After the arrival, Company G engaged a contract organization to deal with the drug development of their main drug candidate to bring the substance from preclinical stage into its first clinical trial. The project ended up with devastating results and for the subsequent years to come, Company G remained stuck in the earlier development stages. In 2004, the present day product development manager (PDM) was recruited, strengthening the internal drug development competence. Within the following year, the main drug candidate was approved by the Swedish Medical Products Agency, and its first clinical trial initiated.

Today, Company G has grown into one of Sweden's largest small pharmaceutical companies with almost 50 employees. Apart from its research department, the organization also handles its own production and has an additional Animal Health operation (not included in the following case description). The company is situated in one of Sweden's largest Life Science centers and has four substances in its Human Health pipeline. One of these projects is currently running its Phase III trial whilst the rest are planned to successively enter their first clinical trial within the subsequent two years.

Discovery and development

Company G has only worked with projects derived from their in-house research activities leading to its four pipeline drugs. The substance developed the furthest was chosen due to its highest improvement potential, and according to earlier market analysis, the future demand of similar substances will most likely increase.

Due to the unsuccessful collaboration between Company G and the Swedish contract organization mentioned above given full responsibility for the main project, an extensive delay was unavoidable. According to the product development manager, the difficulties arose since there was no real drug development competence within the company at the time, and the CRO was not able to deliver. But once the drug development knowhow was recruited

20 This Case is based on an interview with the PDM of Company G (100421) and company homepage materials.

in-house, the project advanced in a stepwise manner. *"We did have other sources of interruptions apart from the failed CRO collaboration, but that collaboration was the main setback in relation to the delay between preclinical and clinical stages,"* explained the product development manager. The other sources of interruptions mentioned included difficulties in recruiting patients and disruptions in manufacturing activities.

The organizational and strategic structure of "pharming"

The overall business strategy of Company G is to develop their projects all the way to the market through partnerships, supporting the final and most expensive stages. Up until now, the company has brought one of their candidates to Phase III trial and is currently working with a partner that will be responsible for marketing and sales in the future market entry. *"It wasn't difficult to find interested partners since they are always out there scanning for opportunities. But it does take a very long time to finalize a contract."* (PDM, Company G). According to the product development manager, the company did not put much effort into profiling themselves towards any potential future partner. Instead, they showcased their offer once they had gathered enough data to do so.

Today, Company G consists of circa 50 people working in its manufacturing facilities, regulatory department, economy department, human resource department, quality department and medical product development department. A few years ago, the company recruited up to twenty new employees within a year to be able to deal with the increased workload of its operations, most of which involved the manufacturing activities. Within the product development department there are currently six employees whereof three were newly recruited when they entered Phase III. *"We have grown larger than we had expected,"* adds the product development manager.

Company G uses consultants mainly when it comes to short-term demands. Since having been involved with "experts" of very different calibers, the bad ones are the ones being remembered. Despite the unpleasant experience with the former CRO, Company G still collaborates with many different contract organizations and the product development manager implies that the quality of delivery differs markedly. *"The contract organizations are very good at not delivering what was promised at an even higher price than initially offered. One really have to keep a close eye on the collaboration process and be aware of what there is to expect."* (PDM, Company G). The product development manager

further implies that there are no major differences between the local and the international contract organizations.

The financial situation of the company

The ownership structure of Company G differs slightly from the typical small sized pharmaceutical company by not involving any venture capitalist organizations. In the beginning, the company was owned by a self-founded holding company selling shares to friends and angel investors. It was a short-sighted funding strategy that ensured their financial capacity for no more than three month at a time. To further finance its operations, Company G started another business alongside its drug development activities in order to secure a continuous cash flow.

Today, only the drug development business is still operating with its activities financed by the public stock market and a partnering deal. The company has chosen not to apply for any grants due to the efforts required without having any prior notice as to whether or not anything good will come out of it. Overall, the financial conditions of Company G have been quite typical: *"Our financing situation has both been up and down. There are times when we have to prioritize, but also times when we're relatively free to do as we want,"* says the product development manager. The PDM also points out that the company have been in contact with a couple of Life Science venture capitalist companies, but chosen not to get involved.

The big picture from the PDM of Company G's perspective

When discussing the four main environmental factors recognized in this study to influence the drug development process in a micro- and small-sized pharmaceutical and biotechnology company, the product development manager of Company G names competence as the most important factor, without neglecting the significance of financing. *"Simply having a good product is not necessarily enough. One has to be able to run the development and market the company in order to move forward,"* argues the product development manager. In relation to the importance of having enough competence within the company, the product development manager also emphasizes the importance of having understanding and focused leaders.