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The Death of the Dinosaurs

A Study about the Innovation Climate in the Pharmaceutical Industry in Region Västra Götaland

Bachelor Thesis

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in Region Västra Götaland

Dinosauriernas Död

En undersökning av innovationsklimatet inom läkemedelsindustrin
i Västra Götalandsregionen

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ABSTRACT

Background: The global pharmaceutical industry struggles to develop innovative drugs that regulatory authorities are willing to approve. The medical need is apparent, especially with the trend of an ageing population. Scientific articles in the medical field depict the current market situation as increasing costs of drug R&D, the increasing number of research sites shutting down, job cutoffs, tougher requirements of documentation and expiring patents of several blockbusters. In order to better comprehend those setbacks this study intends to analyze the situation from an innovation management perspective.

Method: Semi-structured interviews with 13 experts from the pharmaceutical sector in region Västra Götaland were performed to better understand the problem. The answers were transcribed and scanned, ranked after relevance, categorized into themes and extracted to the result.

Result: The term 'pharmaceutical innovation' could be found in most steps of drug R&D. The ulcer medicine Losec was often exemplified as a radical innovation. However, the industry faces numerous obstacles in the race for blockbusters. The innovative climate has changed, resulting in a tougher business climate in many perspectives.

Conclusions: The situation has radically changed: today's business model is unsustainable, affecting the delivering of radical innovations. A paradigm shift might allow for new circumstances, creating new innovation platforms. The Big Pharma will become experts in drug development, while smaller biotech companies will have a primary role in the discovery of radical pharmaceutical innovations in the future.

Keywords: innovation management, pharmaceutical industry, The Big Pharma, paradigm shift, organizational climate, core rigidities, drug development, drug discovery.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Den globala läkemedelsindustrin står inför stora utmaningar då antalet godkända läkemedelsinnovationer har minskat och banbrytande läkemedel tenderar att förekomma allt mer sällan. Vetenskapliga studier pekar på att framtagning av nya läkemedel har blivit dyrare, att kraven från myndigheter är tuffare och att läkemedelsföretagens inkomstkällor har blivit allt torrare i och med stora patentutgångar på läkemedelssuccéer. Detta har i sin tur lett till omfattande nedläggningar av industriella forskningscenter världen över och under senaste tid även i Sverige.

Det medicinska behovet är idag enormt, delvis på grund av att vi lever allt längre och vill vara friskare och delvis för de stora folksjukdomar såsom fetma, som saknar tillräckligt effektiv behandling. Även svårare områden som cancer och demens är i behov av effektiv terapi. Forskning tyder dock på att den traditionella läkemedelsindustrins roll som skapare av radikala innovationer kommer att förändras i framtiden. Denna uppsats syftar till att djupare undersöka problemen i läkemedelsindustrin. Genom att använda managementglasögon hoppas författarna kunna se problemet från ett annat perspektiv.

Denna uppsats omfattar resultat från 13 intervjuer med experter på olika positioner inom läkemedelsindustrin och forskning i Västra Götalandsregionen. Detta med förhoppning att personer som upplever problemet till vardags kanske kan sitta med betydande information om situationen och möjligtvis till och med en lösning på svårigheterna med läkemedels-innovationer.

Resultatet tyder på att terminologin läkemedelsinnovation inte är så självklar. Intervjupersoners definitioner av läkemedelsinnovation kunde inbegripa alla steg i läkemedelsutvecklingen, men även t.ex. förpackning och hantering av läkemedelsavfall. Det går inte komma ifrån att det innovativa klimatet är tuffare, inte minst i Sverige. Stora bolag har blivit allt mer byråkratiska samtidigt som det finns övertygelse att miljöer av frihet och tillåtande är viktiga faktorer för innovationsprocessen. Dagens organisationsmodell är ohållbar och många spår en avgörande omställning där små biotechbolag kommer stå för idé-försörjning medan stora läkemedelsindustrin fokuserar mer på utveckling och marknadsföring.

ACKNOWLEDGEMENT

We would like to show our gratitude for our supervisor Fredrik Lavén for all the useful advice during the writing of this thesis.

We sincerely want to thank our opponents and participants from the thesis seminar who helped us to see and solve some of the issues with the thesis. We also want to show our gratitude to all respondents who were kind enough to spare some of their time for interviews – without you we would not have been able to conduct the study. We truly value this opportunity that you gave us and have tried our best not to expose anyone or wrongfully translate anyone's words.

Last but not least, special thanks go to those respondents who shared with us several articles and ideas/theories about the situation, being at least as enthusiastic about the issue as we were.

Aile Oja and Tai Phan
Gothenburg in June 2012.

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ABBREVIATIONS & DEFINITIONS

Big Pharma	-	Global Pharmaceutical Industry with indicates the biggest pharmaceutical companies.
Blockbuster	-	A drug generating more than US$1 billion revenue per year in sales e.g. Losec.
BRIC-countries	-	Collective name for countries Brazil, Russia, India and China.
Clinical trial	-	The later part of the studies that involves humans, such as healthy volunteers, or patients
Corticosteroids	-	A group of medicines that surpresses inflammation, and has historically been associated with adverse side effects.
EMA	-	European Medicines Agency
Encubator	-	Organisation from Chalmers School of Technology that support inividuals to realize their ideas.
FDA	-	Food and Drug Administration (USA)
Generic	-	A legal copy of the orginal drug, often marketed by other companies after a patent date of expiry. The name is often generic, e.g. based on the pharmaceutics strucure name.
HTS	-	High Throughput Screening, a technology to screen large numbers of chemical substanses.
IMI	-	Innovative Medicine Initiative. Europe's largest public private partership initiative.
IMS	-	Institute of Healthcare Informatics
IND	-	Investigational New Drug Application
Lansoprazole	-	Generic name of a follower drug to Losec
Losec	-	Stomach ulcer medicine, developed by AstraZeneca. Generic name is omeprazole.
Me-too	-	A follower drug to an existing drug in the market, often a strategical action to prolonge a patent or market share. Me-too drugs often only have small changes in chemical structure, drug form etc.
Metoprolol	-	Generic name of the drug Seloken.

mmHg	-	The unit of pressure in millimeters of mercury, used in e.g. blood pressure messuring
NDA	-	New Drug Application
Neurosedyn	-	A sedative drug which was withdrawn from the market in 1961 due to a profile of birth defects across the world. Internationally known as thalidomide.
Nexium	-	A follower drug to Losec, by AstraZeneca.
Omeprazole	-	Generic name of the drug Losec, patented by AstraZeneca
Pantoprazole	-	Generic name of a follower drug to Losec
Payers	-	Authorities and organisations that reimburse and pay drugs for the end users, by tax money or from insurance companies.
Pharmacokinetics	-	The part of pharmacology that is dedicated to analyzing how our body impacts on the drug that we take (as opposed to pharmakodynamics)
Plendil	-	A drug indication of high blood pressure and angina pectoris from AstraZeneca. Mechanism of action is by calcium receptor antagonism. The generic name is felodipin.
Preclinical tests	-	The part of drug development that occurs before clinical trials, including in vitro, in vivo and animal studies
R&D	-	Research and Development
Seloken		A blood pressure surpressor drug by the mechanism of beta-blocker, the generic name is metoprolol.
Thalidomide	-	See Neurosedyn

1 INTRODUCTION

1.1 REGULATING THE PHARMACEUTICAL MARKETS

Hans Rosling has shown with the statistics tool "Gapminder World", how the global health has improved with the increased economical welfare (Rosling et al., 2005). There is also a trend indicating a continuing income increase and health improvement in the developing world (Rosling et al., 2001).

The global spending of medicines is increasing, and was estimated to US$605 billion in 2005 and US$856 billion in 2010 (IMS Institute of Healthcare Informatics, 2011). Historically, the two largest pharmaceutical markets in the world have been the USA and EU. Today, the emerging markets of BRIC-countries - the so-called "pharmerging markets" - may trigger a change in demand for healthcare, should the welfare diseases, currently seen in the western world, strike BRIC-countries. There will also be a change of balance between branded drugs and generic drugs transactions, as the patents of many substantial blockbusters will expire within the next few years. (CBO, 2008, Folland et al., 2010, IMS Institute of Healthcare Informatics, 2011)

Drugs are highly potent products that could be dangerous and harmful (Östholm, 1995). Thus, rules and guidelines in the markets are of significant importance for registration and approval of a drug. In the USA, the market is regulated by Food and Drug Administration (FDA), while European Medicines Agency (EMA) is responsible for the EU market (FDA, 2012, EMA, 2012). In addition, in Europe each country has their own national regulatory authority that is responsible for superintendence and approval procedures, e.g. Medical Products Agency (MPA) in Sweden (Medical Producs Agency MPA, 2012). Also national beneficiary agencies are important for decisions regarding subsidies within each country, e.g. The Dental and Pharmaceutical Benefits Agency (TLV) in Sweden (The Dental and Pharmaceutical Benefits Agency TLV, 2012).

There have been attempts to harmonize the regulations system, for example The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) which strives to harmonize the regulations in the US, EU and Japan to better ensure safety and facilitate the New Drug Application (NDA) registration process (Abraham and Lewis, 2000, International Conference on Harmonization ICH, 2012).

1.2 THE PROCESS OF PHARMACEUTICAL DEVELOPMENT

Drug development is associated with high tech, big risks, long time span and high R&D costs, but has traditionally been motivated by a yearly double-digit return of investment (Folland et al., 2010, Frantz, 2005). The chance to succeed is small to say the least: only one of the discovered 5 000 – 10 000 compounds will get approved and reach the market in the end, see Figure 1 (Dimasi, 2001).

The drug development process consists of preclinical and clinical phases. The preclinical work is focused on understanding the mechanisms and pathophysiology of a medical area of

interest. A bank of compounds and substances of interest are identified with High Throughput Screening (HTS), but very few of the initial substances will pass on to the clinical trials, see Figure 1 (Cowlrick et al., 2011).

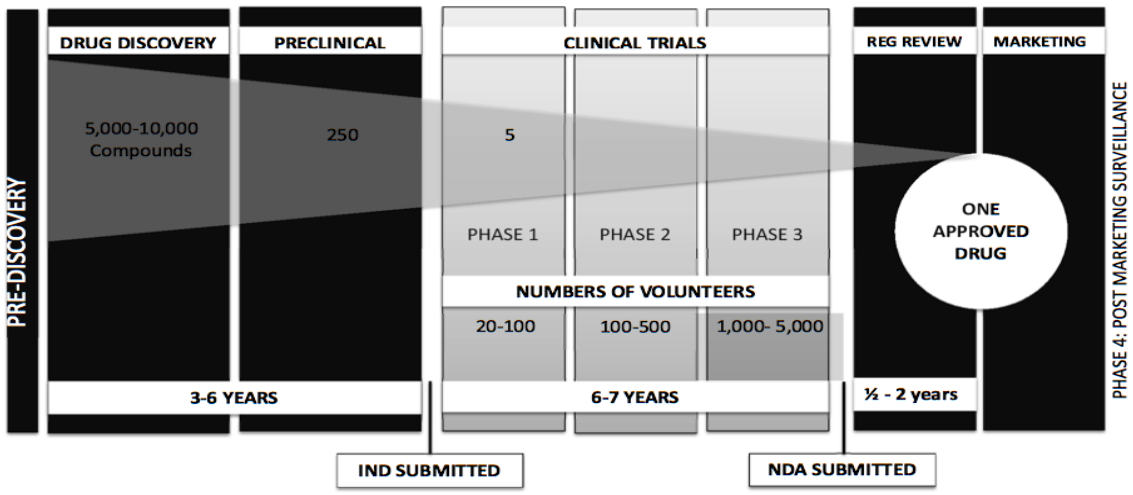

Figure 1. Development process of a pharmaceutical (Adapted from Pharmaceutical Industry Profile, 2009).

Prior to the clinical trials the investigators have to give an approval on the Investigational New Drug application (IND). The clinical trials are divided into three phases where especially phases II and phase III are very costly, due to the study design, the size of patient groups and the area of investigation. Phase I is exploratory and intends to investigate the drug on healthy volunteers as the First Time In Human (FTIH) to observe pharmacokinetics, gather data on adverse events, toxicity data and set the tolerable dose-interval (Lemne and Lafolie, 2009). Phase II trials ("proof of concept"), test the effect of the substance on voluntary patients, to find the optimal dose-regimen and also to map the possible side effects (Lemne and Lafolie, 2009). Lastly, in the clinical phase III, a confirmatory study is performed to document and confirm the drug's effects. The documentation is used to convince the New Drug Application regulatory authorities to approve the drug (NDA). This process of clinical trials can take 6-7 years and is the most expensive part of the developmental process, due to the big study population and the quantity of documentation. At the regulatory authority it can take from ½ to 2 years to review the registration. After an approval the drug can finally be marketed for sales according to the legislation in each part of the world (Abraham, 2003, Lemne and Lafolie, 2009, Cowlrick, 2011).

1.3 THE SETTING

Merges and takeovers are said to be the norm in this industry for the last decades, affecting the size and form of today's pharmaceutical companies. Successful biotech companies in Sweden such as Pharmacia from Uppsala and Hässle from Mölndal are today part of the corporations Pfizer and AstraZeneca (Pfizer, 2012, AstraZeneca, 2012a).

AstraZeneca, where almost all our respondents work, has gone through several organizational changes before it came today's large corporation. In 1954, the large apothecary laboratory Hässle, moved from Hässleholm to Mölndal, Västra Götaland. Astra research laboratories

had acquired Hässle earlier, and already held facilities in Södertälje, southwest of Stockholm. Contacts with the University of Gothenburg later showed the direction that Hässle could approach. In 1954 Hässle's product sales were at US$600 000 but 40 years later the annual turnover reached US$2 500 000 000, product exports accounting for more than 90%. The merge of the Swedish Astra AB and British Zeneca Group in 1999 resulted in the big corporation AstraZeneca with 34 000 employees and a research budget of £602 million. Successes as stomach ulcer medicine omeprazole and heart and blood pressure medicine metoprolol were discovered at the site in Mölndal. Omeprazole was a result of 20 years of difficult work and is recognized as one of the most sold drugs in the world, utilized by more than 100 million patients all over the world. In 2011 AstraZeneca sales were US$33,6 billion, and the corporation had 57 200 employees (AstraZeneca, 2012b). (Östholm, 1995).

AstraZeneca recently announced cutting over 1000 jobs due to the research center shutdown in Södertälje (Andersson and Malmström, 2012). Only two years earlier research center in Lund was shut down, with around 900 layoffs (Andersson, 2010). However, this is not an exception – since year 2000 around 300 000 employees have been dismissed from the pharmaceutical industry, and the rate of job cuts per year has increased, see Figure 2 (Herper, 2011) (Andersson and Malmström, 2012).

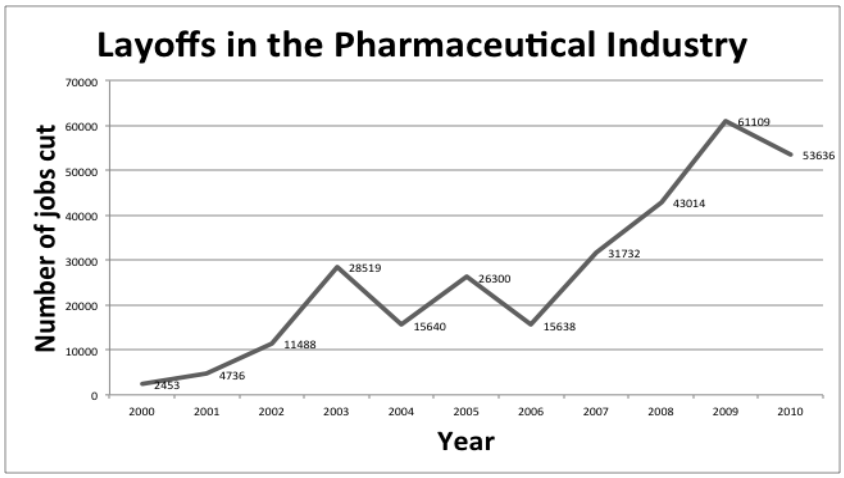

Figure 2. A Decade In Drug Industry Layoffs (Herper, 2011).

1.4 THE 'BIG PHARMA' PROBLEM

Historically recognized as 'the Big Pharma', the global pharmaceutical industry has been a flourishing sector, primarily due to inventions of important pharmaceuticals that satisfy unmet medical needs (Arrow, 2001). The pharmaceutical industry has a special relation to innovation, as of being very dependent on both successful R&D and available large-scale investments. Innovation in this industry has been a topic in many scientific articles and there are several studies recognizing innovation struggles in Big Pharma (Hedner, 2012, Cowlrick, 2011).

Research Spending Per New Drug	
Company	R&D Spending Per Drug
AstraZeneca	11,790.93
GlaxoSmithKline	8,170.81
Sanofi	7,909.26
Roche Holding AG	7,803.77
Pfizer Inc.	7,727.03
Johnson & Johnson	5,885.65
Eli Lilly & Co.	4,577.04
Abbott Laboratories	4,496.21
Merck & Co Inc	4,209.99
Bristol-Myers Squibb	4,152.26
Novartis AG	3,983.13
Amgen Inc.	3,692.14

Figure 3. Spending in $ Million (USD) (Herper, 2012).

Radical pharmaceutical innovations have gotten difficult to attain and have evidently declined during the last decades (Munos, 2009). The past drug disasters, like with thalidomide, play a part in this, because they have caused today's strict regulatory system and safety concerns - many of the earlier drugs would never be approved today (Abraham, 2003). The R&D cost to deliver one drug to the market has rapidly increased (DiMasi et al., 2003, DiMasi and Grabowski, 2007). Adams and Brantner estimated that the average R&D cost of developing a new drug in 2006 ranged from US$500 million to US$2 billion. More recent statistics show average costs per drug being around US$4 billion, with AstraZeneca at the top with an R&D spending of nearly US$12 billion per launched drug, see Figure 3 (Adams and Brantner, 2006, Herper, 2012). With such problems, there is a need for change or improvement. Therefore it is stated that the global pharmaceutical industry, earlier known as the Big Pharma, is about to change (Hedner, 2012).

With budget constraints and requirements of health economic considerations, the decision-makers in this industry need to allocate resources rationally and optimally. However, decision-making here is not taken in a straight "go or no-go" line of decisions, but is much more complex. As was in the case of Losec®, projects may face numerous setbacks, but one unexpected turn of events could bring the project to success (Östholm, 1995). A survey showed that decisions based on the same information from the pharmaceutical industry still tend to vary significantly among decision-makers (Cowlrick et al., 2011).

Public-private partnership has historically been a part of industrial research strategy which has given birth to many medical inventions, such as in the case of Losec. However, in our time this cooperation has grown weaker, not the least because globalization is creating new cooperation possibilities. Besides globalization, as the pharmaceutical industry became wealthy, expert researchers were employed by the company, and therefore no longer required external research support (Östholm, 1995). Stevens et al have, however, shown that the public sector has an important role for medical innovations, such as contributing to vaccine R&D (Stevens et al., 2011). The attitude of the Big Pharma is likely to change, resulting in more openness and collaboration with other organizations (Hedner, 2012).

Many agree about how complex the drug discovery process can be. Risk-to-benefit considerations is one factor that the decision makers in the drug industry have to face in their daily work (Cowlrick, 2011). Pammolli et al mean that the decline in successful innovations is apparent because of companies focusing more on high-risk projects. However, if companies only chose projects with high possibility of success, this would mean a fierce competition (Pammolli et al., 2011). Thus, taking on a high-risk project can be more profitable for a company. One example of such high-risk project is the drug research in neuroscience, which has turned out to be very difficult (Kneller, 2010).

There are different opinions on how to handle the situation. A more accurate selection of candidates which are suitable for studying is of great importance in order to effectively manage the invested capital (Pritchard et al., 2003). Also, the ability to shut down doomed projects in early phases is of high relevance to cutting costs (Arrowsmith, 2011b, Arrowsmith, 2011a). Mikael Dolsten, the global director of research at Pfizer wants to decrease Pfizer's research budget of US$9,4 billion and explains that money itself cannot bring more drugs to the market (Wahlin, 2011). Additionally, Jean-Pierre Garnier, the CEO of GlaxoSmithKline suggests that the companies "break up their giant R&D organizations, overhaul core processes, and put passionate scientists back in charge" (Garnier, 2008).

1.5 INNOVATION AND INNOVATION MANAGEMENT

Despite of the attempts to analyze and control innovation processes, we believe there are and probably always will be several factors that prevent innovation. The question is whether there is something more beyond the typical "problem – how to fix it"-perspective. Does every problem have a straightforward solution or even a satisfying explanation? Thus, we recognize the need to take a closer look to today's pharmaceutical business, with the help of innovation management theories.

As mentioned earlier, the pharmaceutical industry has a special relation to innovation, where the latter could truly be seen as "the engine of growth" (Trott, 2012). But what is innovation and what is innovation management? We will show in the theoretical framework and in our analysis that this is not so clear. Our theoretical framework includes the definitions of innovation, the important aspects of innovation, and innovation management perspectives from Burns & Stalker, Tidd and Leonard-Barton.

1.6 AIMS AND RESEARCH QUESTIONS

Radical innovations have been of great importance for the pharmaceutical industry. Within this field of research, numerous scientific articles and reports present the problem, trying to figure out the underlying problem and give a solution. This study objective is to reach out to and listen to experts such as representatives from the Big Pharma and the researchers. We limit our work to analyzing one of the world's biggest pharmaceutical companies that is partly located in Sweden, Västra Götaland.

The aim of this thesis is thus to explore the innovation climate in today's pharmaceutical industry, and to draw conclusions from both previous studies and theories but also from the insights we will gain during the interviews.

- What innovation difficulties are apparent in the Big Pharma's innovation climate?
- What are the possible reasons for these difficulties for the Big Pharma and is there any solution?

2 THEORETICAL FRAMEWORK

2.1 DEFINITION(S) OF INNOVATION

The crucial part of this study is about innovation – but what exactly is an innovation? Taking a closer look at the definitions reveals that there is some maneuver-space within the boundaries of definitions. Trott means that the problems arise due to two different approaches where innovation is seen either as an event or as a process (Trott, 2012). Furthermore, some definitions recognize that an innovation has to be implemented in order for it to count as a (successful) innovation.

'Innovation … is generally understood as the introduction of a new thing or method ... Innovation is the embodiment, combination or synthesis of knowledge in original, relevant, valued new products, processes or services' (Luecke and Katz, 2003).

'All innovation begins with creative ideas /…/ we define innovation as the successful implementation of creative ideas within an organization /.../ creativity by individuals and teams is a starting point for innovation; the first is a necessary but not sufficient condition for the second' (Amabile et al., 1996).

Trott means that innovation should be seen as a series of activities, involving the following three aspects: response to the context-dependent need or opportunity, effort that can result in something new and the need for further changes (Trott, 2012).

Furthermore, Trott states that context has to be taken into account, because in different environments, times, viewpoints or for different people, innovation can be seen very differently (Trott, 2012). To complete this, Tidd and Bessant state that seeing and understanding innovation from any single viewpoint, for example seeing innovation purely as R&D, can cause problems and limitations in the firm's innovation management. In this study we follow Trott's definition, but we take into account our respondents' views on what an innovation is.

Tidd and Bessant add that one can distinguish between incremental and radical innovations, where radical innovations are "new to the world", including completely new technology such as steam power or bio-technology. Furthermore, there are different stages where innovation can be used: product or service innovation, process innovation, position innovation, paradigm innovation (Tidd and Bessant, 2005). By using this distinction, our aim is to see in which stages innovation process is present in the pharmaceutical industry.

With innovation, there are always risks connected; they can be of operational, financial, or commercial nature. Operational risks, as the name says, are connected to the operative processes, and related to, for example, cost, launch, and even company's reputation or brand. Commercial risks can be tied to consumer or competition, and finally the financial risks are about investment-related risks (CIMA, 2007). We believe that risk, no matter its nature, has an impact on the situation that we are studying.

2.2 INNOVATION MANAGEMENT

2.2.1 DEFINITION

Researchers see innovation as a management process (Tidd and Bessant, 2005, Trott, 2012). Innovation management is defined by us as the various processes that can be seen as crucial in order to manage the organization's innovation. Trott means that innovation should be seen as a process, and not a single event (Trott, 2012). It might be hard to study innovation management completely separately; for example, Trott (2011) means that other management areas should be included in the big picture, such as new product development.

Furthermore, innovation management might differ within industries. According to Trott, the pharmaceutical industry is more characterized by technology-push model, see Figure 4. Compared to market-pull model, in technology-push the process is linear, being "pushed" by the technology (R&D). Another difference is that the market-pull model is based on the market needs, whereas technology-push might not have the market need as its primary push factor (Trott, 2012, Martin, 1994).

2.2.2 INNOVATION IN ORGANIZATIONS

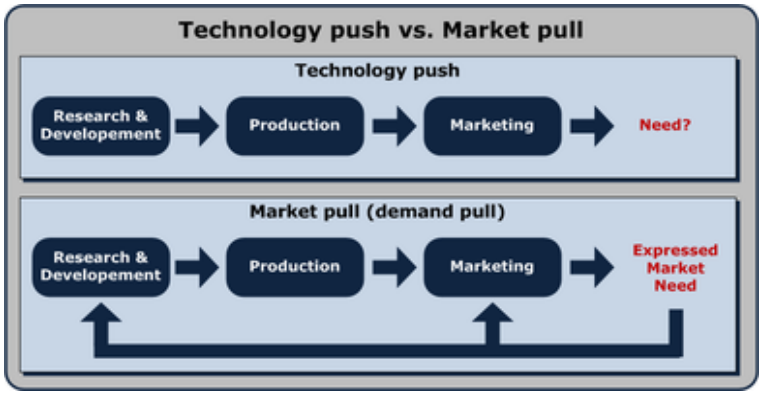

Figure 4. Schematic presentation of technology push and market pull (Adapted from Martin, 1994)

In order to better recognize and understand the problems and complexity of innovation and innovation management, we focus on literature that analyzes the role, responsibility and future in the organizations, regarding innovation processes and innovation management.

Already decades ago, researchers began to notice the complexity of innovation as the organizations became more complex and technically advanced. In the classic book *The Management of Innovation*, Burns and Stalker describe how the technological changes and development traditionally has taken place through different time periods, with help of mostly short term goals and ambitions, often initiated by a minority – a small group of people, whose interest these changes will primarily serve. But today innovations are produced by employed professionals, who work in industrial firms, governments, or in institutions that are funded by one of the previous two (Burns and Stalker, 1994).

Burns and Stalker mean further that as the innovations are made faster and faster, it is increasingly more important for companies to support their R&D more and more. Of course, innovation includes risk, according to Burns and Stalker, either this risk is imposed on the individuals or on the organizations. Risk-taking might not be easy, but in changing environments one might have to weigh the risk of change against the risk of not changing anything – the last one can sometimes indeed have even worse consequences, threatening the survival of organization (Burns and Stalker, 1994).

Today, the R&D has said to have changed enormously compared to no more than 50 years ago (Trott, 2012). Trott summarizes the three primary reasons for this rapid development:

- technology explosion, meaning that 90% of our technical knowledge derives from only the past 60 years
- shorter technology cycle, which means that companies have to focus more on new product development
- globalization of technology, which means bigger knowledge transfers due to the licenses and strategic alliances

(Trott, 2012)

In the pharmacy industry, protecting intellectual property is a central issue in order to guarantee the company's revenue, market position, or perhaps even survival. According to Trott (2011), patent expiration dates and the lengthy drug development make it harder for the companies to become interested in new product development. The expiration dates and generic drugs entering the market can according to Trott (2011) decrease the company's market share from having been at 80+% to as low as 10%. To compensate for this, patent extensions are used in Europe since the 1990-s, however the big pharmacy companies have also been accused of using this possibility just to boost profits. Even a month of additional patent time can mean hundreds of millions of dollars in additional income (Trott, 2012)

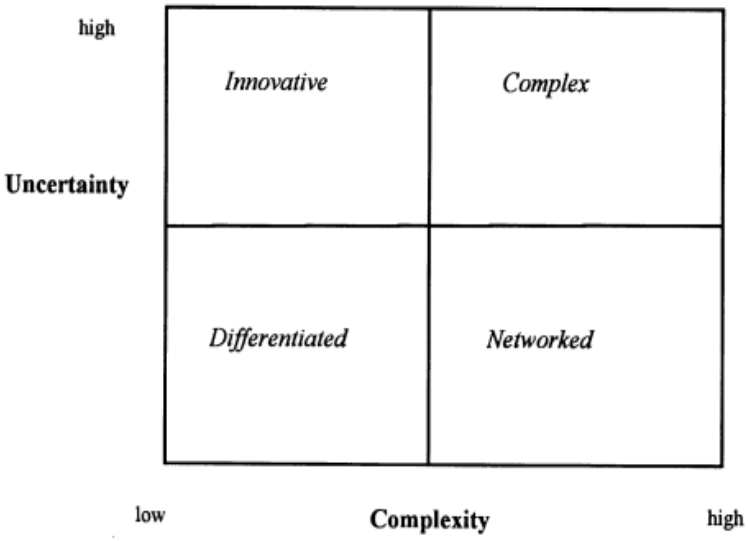

Figure 5. Effect of uncertainty and complexity on the management of innovation (Adapted from Tidd, 2001)

The question remains, do the patents prevent or help innovation? According to Trott (2011), most firms today use patent system to prevent other firms copying or using a technology, which is definitely not stimulating the innovation. Trott means that the initial aim of patent system was to encourage innovation; however it is now mostly used in a preventive manner (Trott, 2012).

2.2.3 COMPLEXITY AND UNCERTAINTY IN INNOVATION MANAGEMENT

Tidd is critical about the earlier innovation management research, by means that it has failed to provide clear advice for managers: the very people who would benefit a lot from this research (Tidd, 2001).

Tidd then provides a model for understanding the dynamics of environment, organization and performance, which could also be seen as a model of understanding threats to innovation in

that specific field or firm. This model is constructed of four quadrants which can cause different issues, and thus might require different organizational structure and processes to manage innovation, see Figure 5: (Tidd, 2001).

In the differentiated quadrant, both uncertainty and complexity are low and the focus is on product/service differentiation, requiring marketing competencies. These are typically fast-moving consumer products.

The innovative quadrant contains high uncertainty but still low complexity. As the name might hint, scientific/technological skills are very important, and there is a functional structure, e.g. pharmaceuticals (Tidd, 2001).

The networked quadrant has low uncertainty, but high complexity, so there it is important with the project management competencies. Transport is one of examples of networked system. Lastly, complex organizations have high uncertainty and high complexity, which puts a range of requirements on this type, such as flexibility and adaptation or learning. Given examples for complex systems is using software in transportation or telecommunications.

Furthermore, Tidd enhances the importance of the degree and type of management when analyzing innovation management. This is shown in the Figure 6, and has three degrees and three types of innovation. Additionally, it is emphasized that *"traditional models of product and process innovation life cycles suggest a shift from product innovation to process innovation, and from radical to incremental innovation as an industry matures"* (Tidd, 2001). The three innovation degrees are disruptive, radical and incremental where radical would mean completely new discoveries (Tidd, 2001, Tidd and Bessant, 2005). Different innovation types are process, product or service innovations. Traditionally one has been able to separate between process and product service, but the distinction can be blurred (Tidd, 2001).

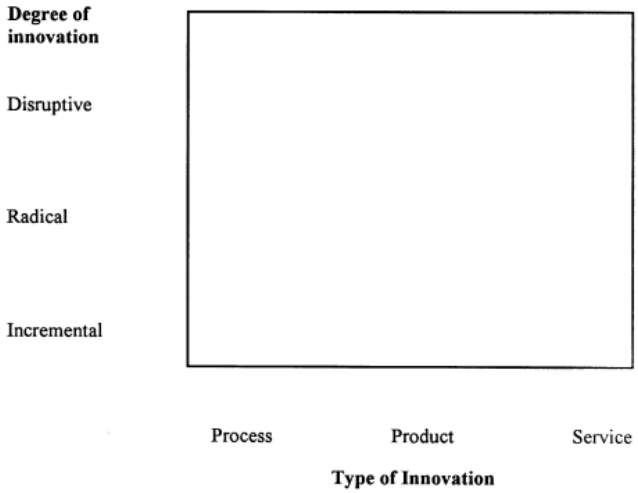

Figure 6. Innovation "space", the degree and type of innovation (Adapted from Tidd, 2005)

So how does an organization respond to complexity and uncertainty? Tidd (2001) mentions two factors that can affect the company's ability to develop or sell new products or services:

- the internal organization, meaning functional links and business divisions that are based on product-market connections
- the external links with other organizations (suppliers, customers or collaborating networks)

(Tidd, 2001). Regarding multi-divisional companies, this organization form has its strength in diversifying products. These companies can be seen as effective innovators if one measures

patents or new products per R&D expenditure (Tidd, 2001). Furthermore there is a possibility to centralize research and decentralize product development for each division. But this structure can limit the range of new competencies within the firms. Thus, multi-divisional firms are seen as those who deepen their capabilities, whereas firms which have fewer divisions are seen as more capabilities-broadening ones (Tidd, 2001).

Regarding the external links, Tidd (2001) points out the importance of networks. According to Tidd (2001), a network is more than just bilateral relationships: it contains both opportunities but also difficulties for the firms. This perspective is thus concerned with how the context, the information flow and also positions of different actors affect networking and collaborations (Tidd, 2001). Tidd also means that the network process is path-dependent – once started, the collaboration is most likely to continue.

A study of 53 research networks found two different ways for the networks to form and grow. The first is an "emerging" network through environmental interdependence and shared interests. The second is an "engineered" network appearing through some triggering entity; no attention is paid to the environmental interdependence or shared interests (Tidd, 2001). Tidd concludes with a suggestion that the complexity and uncertainty of the environment affects the degree, type, organization and management of innovation, and that the greater the fit between these factors, or the more coherent the configuration, the greater the performance (Tidd, 2001).

2.2.4 THE PARADOX OF CAPABILITIES AND RIGIDITIES

Leonard-Barton's theory provides a different, but interesting approach – namely, that there is a seemingly natural paradox in the traditions and values and capabilities of a firm which may cause the firm to be rigid and preventing successful innovating (Leonard-Barton, 1992). Leonard-Barton (1992) means that where there exist core capabilities, there will also be core rigidities to take into account. The definition of knowledge-based core capabilities according to Leonard-Barton is that it is a knowledge set that distinguishes and provides a competitive advantage.

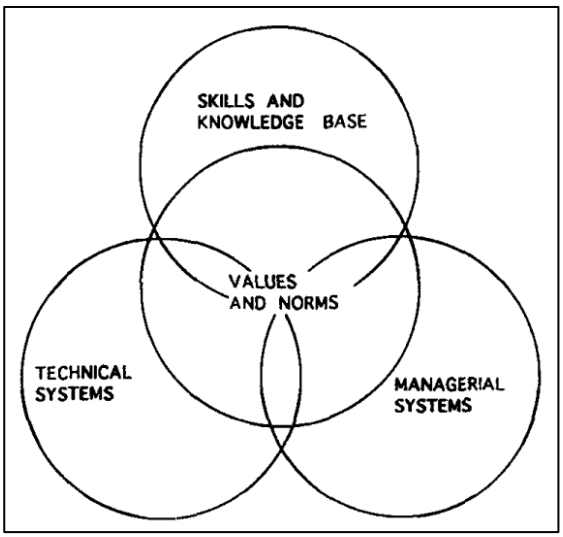

Figure 7. The four dimensions of a core capability (Adapted from Leonard-Barton, 1992)

Leonard-Barton shows also the four dimensions of core capabilities – technical system, skills and knowledge, management system, values system, see Figure 7. The core capabilities are traditionally tied to the fist products or technologies, something that has perhaps developed over a long time; they are seen as institutionalized and "taken-for-granted" part of the firm (Leonard-Barton, 1992).

Neither the ideas of core capabilities nor the importance of managing changes in order to survive are new, as Leonard-Barton shows in the theoretical part of the article. However, it is important to see the eventual conflict in, on one hand innovation appearance, the need for change, and on the other hand keeping the company's current core abilities. Innovation can change the position or strength of these core abilities (Leonard-Barton, 1992).

From the four dimensions of core capabilities, also the core rigidities can emerge. The core rigidities that appear are complex because of both the number and dimensions, means Leonard-Barton. In skills and knowledge-dimension, the rigidities would mean that the firm, even if being good in some dominant discipline, they might be less skilled and weaker in other, less-dominant disciplines. Also the technical systems, if not updated effectively and fast, can pose as rigidities. Regarding managerial systems, seeing project managing as "not a real job", is one of the rigidities. Besides that also the values and norms are important – Leonard-Barton here means simply that the values, norms or attitudes that do support a core capability and enable development can also prevent it (Leonard-Barton, 1992).

Regarding how to handle the rigidities, Leonard-Barton has observed in the study four ways of coping with the rigidities: abandonment, recidivism, reorientation and isolation. Furthermore, it is not easy to create or accept change (a paradigm shift), as also this can become a challenge: Pfeffer means that "'paradigms have within them an internal consistency that makes evolutionary change or adaptation nearly impossible' (Pfeffer, 1982) Still, Leonard-Barton concludes with a thought-provoking sentence: "technology-based organizations have no choice but to challenge their current paradigms" (Leonard-Barton, 1992).

2.3 OTHER THEORIES OF RELEVANCE

Previously mentioned theories are compatible with several other theories, such as those of Christensen (1997) and Hannan and Freeman (1977). This proves that the ideas of existing paradoxes and survival of organizations are widespread. Christensen in his book *The Innovator's Dilemma* means that the successful companies' internal environment often sets stop for producing more radical innovations, and thus smaller start-up companies have an advantage (Christensen, 1997). With other words, just as Leonard-Barton meant, successes and capabilities can become rigidities, obstacles. What is interesting is that the described phenomenon of small successful companies growing bigger and ineffective, to then be beaten by new start-up companies seems like a lifecycle or natural process in the business world.

Hannan and Freeman have rather similar viewpoints in their article *the Population Ecology of Organizations*, such as that the organizations survive in a similar manner to survival of the fittest (Hannan and Freeman, 1977). Thus, meaning that it plays little role to how successful a company has been or currently is, nor does it matter what strategy it chooses – in the end, the ones who survive are these most fit to the changes in surrounding environment (Hannan and Freeman, 1977).

Another important point in this theory is that of shifting environments, meaning that the ability to survive might depend very much on what is happening in the external environment,

and depending on the shift, an organization that survived at some point, might have challenges lying ahead at the other point (Hannan and Freeman, 1977). We conclude that the selected theories are useful in the chosen combination, tackling the problems that are very relevant in today's pharmaceutical industry, and furthermore there are several other applicable theories that can help to study this issue even further.

3 METHODOLOGY

3.1 CHOICE OF METHOD

Research strategies are traditionally divided into two bigger groups - quantitative and qualitative. Quantitative methods are seen as measuring and objective, whereas qualitative methods are explorative, deep-going, and interpretive, often aiming to create a new theory or to deepen and develop an existing, but unsatisfying theory. With other words, quantitative methods are targets for objectivism, and qualitative methods are used to construct (Bryman, 2008, Svensson et al., 1996). For this study we found the qualitative method suitable, because the aim was to identify medical innovations, explore and describe the innovational situation and thus difficulties with innovations. Since this topic can be very subjective, depending on the researcher's interpretation, qualitative interviews seemed like a logical choice of method.

There are some things to take into account regarding qualitative studies. It is often seen as being too subjective and there is the possible lack of transparency which means that it can be hard to see how the researcher carried out the research and made his conclusions. Third, there are problems with external reliability and validity, see 3.3. (Bryman, 2008, Bryman and Bell, 2011). We tried to counter the mentioned problems by having a detailed methodology that shows how we conducted the research.

3.2 COLLECTING DATA

3.2.1 QUALITATIVE PRIMARY DATA

There are different types of collecting qualitative data, for example interviews, focus groups, observations, field studies and document studies (Bryman, 2008, Svensson et al., 1996). We have used qualitative, semi-structured interviews for collecting our primary data. Qualitative interviews are primarily used to identify or discover phenomenon, characteristics or meaning of things either not known to us before or missing a satisfying explanation. The interviews are thus non-standardized, exploring, with the researchers having an active role. (Bryman and Bell, 2011, Svensson et al., 1996).

The semi-structured interviews were a logical choice because we had a certain aim, having defined a couple areas of interest. However, the respondents were given quite a lot freedom in their answers. (Bryman and Bell, 2011). In practice it was quite hard to separate a structured and less structured interview. Still, the interviews were successful, with deep, rich insights and many of the respondents described interesting, original ideas. Thus, we believe we succeeded well by using this method.

3.3 INTERVIEWS

3.3.1 SELECTION OF RESPONDENTS

Snowball-sampling, a non-probability method was used for selecting respondents. Several relevant people were contacted, who in their turn made further recommendations. Such chain of activities creates a constantly growing snowball-like effect. Our method resulted in a total of 13 interviews booked, 6 declines and 4 unavailable/no response, see Figure 8. We conclude that in this case snowball-sampling was an effective method.

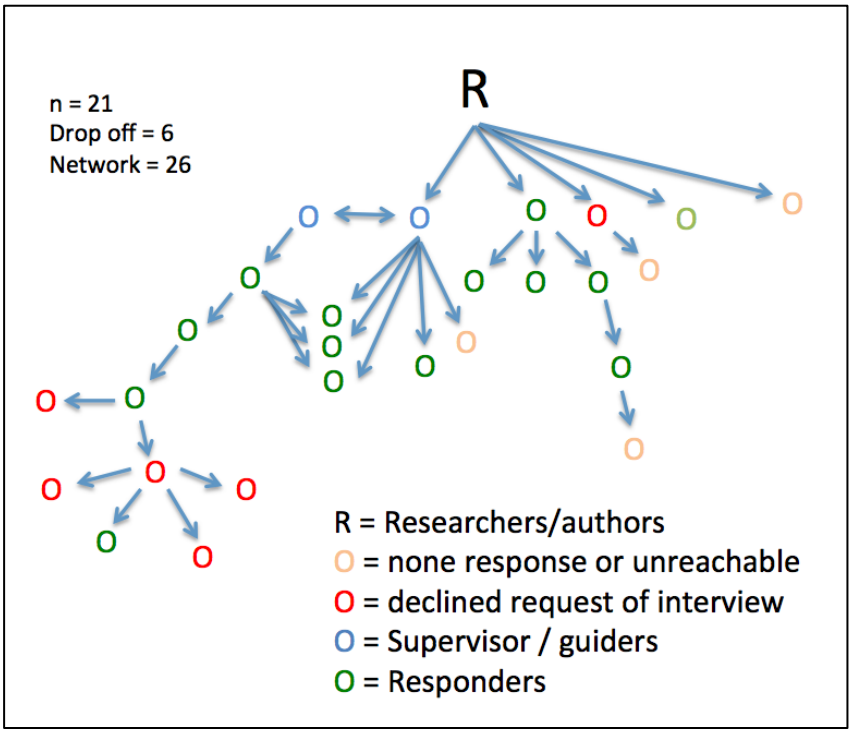

Figure 8. Map of the snowball method.

Many respondents have Ph.D. backgrounds and all have some sort of university degree: Ph.D. in biochemistry, Ph.D. in chemical technology, Ph.D. in chemistry engineering, mathematics, Ph.D. in biochemistry engineering, Nurse, Master in BA, Ph.D. in pharmacy, Ph.D. in biology, and M.D.

They hold several titles: general manager, group manager, market executive, line manager, project leader, director, former executive officer, head of department, members of the boards, disease area director, researchers. Among the respondents' work tasks there were: coordinating, preclinical (LO), marketing, teaching, clinical development, business development, research. We want to point out that several respondents have held more than just one of the positions, e.g. researchers, advisors, managers.

The eventual problem with this selection is that respondents might not represent a wide range of views. However, this study is not meant to cover a whole "population", the industry. By means of these people's institutional knowledge and experience, these people are utterly relevant for this bachelor's thesis.

The interviewees are anonymous, meaning that the readers will not know who was behind which statements. Based on the overlapping answers on the most important questions, our crystal-clear conclusion after writing the result is that the respondents' positions, be it former CEO or a middle manager, play little to no role in the outcome of the result. That due to the various tasks they have held during their career. We are strongly against personalizing the answers more than we already have done because we do not see value in this. It risks the

anonymity, it makes the respondents falsely seem to be played "against each other", and there is no valuable conclusion to be made, that would somehow contribute to our findings.

3.3.2 FORMULATING AND CARRYING OUT THE INTERVIEWS

Kvale and Brinkmann's book *"InterViews: Learning the Craft of Qualitative Research Interviewing"* (2009) was used for preparing for the interviews and forming the questions. As mentioned above, semi-structured qualitative interviews still require at least a light structure (Svensson et al., 1996, Kvale and Brinkmann, 2008). Thus, a checklist was used during the interviews, see Appendix. During preparations, we focused on creating logically connected general questions that were flexible and not leading.

All but one interview took longer than the planned 45 minutes, the longest being 95 minutes. This could mean that 45 minutes was not enough - or perhaps that the respondents opened up and really got in to the talking. Due to the time constraint we didn't plan any follow-up interviews, but were encouraged by many interviewees to re-contact them if needed.

3.3.3 PROCESSING OF THE DATA – COMPILATION AND ANALYSIS

The interviews were recorded both with cell phone and the digital recorder. The interview material was 14 hours, taking 60+ hours to transcribe. Even though we started transcribing right away, we did not have time to transcribe the last interviews fully.

The transcribed answers from respondent were ranked in four level of importance and distributed in categories of theme. The highest rank would mean information that was directly tied to the questions; the lowest rank would have the least relevance. Reasons for ranking were that the material was too big for a standard Bachelor thesis, so a selection had to be made. Also not all the information was relevant or useful. That was mainly due to the qualitative nature of studies where respondents sometimes talked about less relevant things. The two authors together did the ranking work, one of them having a perspective and background as Master in Pharmaceutical Science, which we believe increases legitimacy to carry out such selection work.

3.4 RELIABILITY AND VALIDITY

In scientific studies, it is important to be aware of the quality requirements placed upon the research – the most common criteria are reliability and validity (Bryman and Bell, 2011).

3.4.1 RELIABILITY IN QUALITATIVE RESEARCH METHODS

External reliability means the degree to which a study can be replicated. Due to the nature of qualitative research, it is likely to be a tough-to-meet criterion. On the contrary, internal reliability recognizes how well the research group members share or agree about what they see or hear (Bryman, 2008, Bryman and Bell, 2011, Svensson et al., 1996). External reliability in this study can only be controlled through a replication. Regarding internal reliability, we discussed a lot of things, for example we had a serious discussion about what we actually are writing about, what do we want to find out, how can we make the best interview questions, which things are relevant etc. This, we believe, has increased the internal reliability of our work.

3.4.2 VALIDITY IN QUALITATIVE RESEARCH METHODS

External validity refers to how well the findings can be generalized or expanded to other settings. That has shown to be problematic, because qualitative research often uses case studies, small samples, and specific environments. Internal validity on the other hand is seen as one of the strengths in qualitative research, having a purpose of testing whether there is a good match between the observations and developed theories (Svensson et al., 1996, Bryman and Bell, 2011). We understand the problem with external validity, but it would require opinions of other researchers regarding our result being applicable elsewhere.

4 RESULT

Note: The result includes only the opinions of respondents, not the authors.

4.1 THE INNOVATIONS IN THE PHARMA INDUSTRY

4.1.1 WHAT DEFINES A GOOD INNOVATION IN THE PHARMACEUTICAL SECTOR?

One respondent meant that words like 'innovation' can mean very different things to different people. Regardless, the most common opinions were that innovation is a new drug or the process of developing a new drug (some or all parts of the process). One former executive stated that the finest one can achieve in this industry is something that is called "first in class" – a drug based on completely new mechanism that can also cure more effectively. First in class drugs are rare today, according to this respondent.

An innovation was seen by many respondents as something that can help or cure the patient and thus benefits the society. It was said, for example, that "The proof is in the pudding - an innovation is always in the eye of the beholder" and "in a way, it is the market or the patient who defines the success of a drug." Losec was mentioned several times as a commercial and medical success - it brought an entirely new way to attack a whole disease area, so there is almost no need for gastric ulcer surgeries anymore. This kind of drug has helped the society to save finances, for example with the shorter sick leaves.

One respondent stated, "It is the doctor and the patient that recognize the drug as something that has made difference: on one hand the patient's everyday life and the other hand given the doctor the chance to help others by prescribing this pharmaceutical drug. Then this innovation has been accepted not only on the paper by the regulatory authorities, but by the rest of the world." Thus, a patent by itself is no innovation, it is only a discovery.

A senior manager meant that innovation can be found in areas such as marketing, too, for example positioning and profiling the product in the best way. One researcher agreed to that and meant, "Creativity within the pharmaceutical industry does not happen only at some synthesis department, it's there throughout the whole drug development process". The work around drug innovations is also very important, for example improving compliance and adherence in treatment. Furthermore, aspects such as environmental impacts were mentioned. "A really good innovation is thus to discover a molecule that can make it all the way through

filters and pitfalls, it is innovative to try and lay this puzzle," was one thought that summarizes the issue.

4.1.2 THE QUALITY OF AN INNOVATION

The last 10-15 years the new drugs only brought marginal improvement, one respondent claimed. Today it is very important to be the first to release a new innovative drug; this was not the case earlier. An example of blood pressure medicines was given, namely that there are maybe 10 drugs that lower blood pressure - so to develop yet another one, even if it had a novel mechanism, would not be a good innovation because it won't have much of an impact. According to one senior principal scientist, views on me-too drugs have also changed - the payers are not willing to reimburse me-too anymore so these drugs start to disappear. The respondent was positive to that: ***"One should not waste billions of dollars only to develop something with very marginal improvements."*** This change is seen as something that would make people to be more innovative.

In case of Losec many would agree that this was a very innovative drug. After that there came other gastric ulcer drugs like Nexium and then Lansoprazole and Pantoprazole that are giving very good yield. "The researchers "twisted and turned" one drug and tried to find small differences/advantages that would then be marketed very intensively," one respondent explains. Another respondent, a former scientific advisor, says also that the investing in marketing and sales is today twice that of R&D: "The R in R&D has thus disappeared and we only have D left - but it is the research that creates innovations, not development".

"A really good drug innovation happens on the day when a patient or their relative calls or writes to you and thanks you for saving their life and giving them a future. These letters are golden," says one respondent. "An innovation is something that no one has done before; you do something that is better and really appreciated."

4.1.3 IS IT POSSIBLE TO AFFECT THE INNOVATIONAL WORK?

The shared opinion is that people with open minds, who do not ignore unexpected findings, have created the biggest innovations. "It is of importance to have the ability to think outside the box, to discover new opportunities, and to produce an innovation, but at the bottom it is the process behind achieving a new mindset which is of importance," one researcher states.

4.1.3.1 THE ABILITY TO SEE WHAT OTHERS DON'T

One respondent said that sometimes the market has to be created (like Viagra, hair loss therapy), which might be seen as something "ugly". But sometimes there are diseases or syndromes that don't have a name yet or are not fully understood scientifically, so one can try to learn about it in order to then build a market. According to respondents, it is often the Big Pharma companies that see the new possibilities, such as the case with asthma being an inflammatory disease and by doing so have radically improved the quality of life for asthma patients. "To be able to plant something new, one has to prepare the soil first," was another opinion from a senior manager.

"It is the ability to see the small things in order to create bigger things", "to see that little extra something that no one else sees at this moment" are how our respondents explained this ability. Seloken (Metoprolol) was given as example of another very good innovation. But this was created by people outside the company – Åke Hjalmarson and Finn Waagstein, the researchers in Gothenburg that had realized that one could give beta-blockers to patient with heart failure.

Innovative mindset is a returning phrase during the interviews. One senior manager said that this mindset can be achieved in an environment that is more allowing towards all involved people. He made the following comparison: "For example grandmothers are usually more allowing than mothers. So ***a grandmotherly-environment that allows you to test more things: this could be transferred into the manager's situation where one can let people think freely and not hold them down by saying "no". You let it bubble."***

In the case of Losec the researchers did not cancel the drug development; they just found other ways to do it. These people managed to see what others did not; they were entrepreneurial researchers who had the ability to think in new ways in order to solve a problem. One researcher meant that economists often get the blame for setting the stop for innovation. It is important for economists to understand their role in innovation as well. As a creator or innovator or entrepreneur one has the ability to translate what innovation means. And in this transfer ***one can also show what it will yield, not only what it will cost.*** One manager meant that perhaps we underestimate the gut feeling or importance of simply getting lucky. Others agreed that randomness and luck indeed play role in the innovation process, whereas one (middle manager) said "well, I hope it doesn't play any big role", seeing randomness more like a threat to stability.

4.2 THE PHARMACEUTICAL SECTOR

4.2.1 HISTORICAL SITUATION

Historically, the pharmaceutical industry was recognized by our respondents as successful, original and consisting of small local organizations. One middle manager meant that, "We had good years when we started, golden years, and there weren't so many requirements from the authorities." The strategy back then was to place research sites and units near the big Swedish universities in Uppsala, Gothenburg, Malmö and Lund.

Several of the respondents mentioned the impact of the academy back then: there was an open collaboration and exchange. The old times were described in positive terms. Drug after drug came out to the market and became great successes. The R&D technologies flowered at the same time as the important medical achievements were reached. The blockbusters gave an incredible yield for investors and the companies were able to grow bigger. At the same time when the local pharmaceutical companies became global, the industry as a whole got the name "the Big Pharma".

The bigger organizations have however a reverse side because they are central and slow to lead. This can be seen as a leadership question, as one researcher stated: "by definition the

big organizations are harder to lead than the small ones." Another researcher meant that "The climate within the industry got tougher and the golden times for the Big Pharma is now seen as history." It was also mentioned that the latest 10-15 years has brought consolidation of the industry, meaning many takeovers or merges. These took place in hope to overcome the reduced revenues and potential financial problems due to patent expirations, according to a former executive.

4.2.2 DIFFICULTIES WITH THE DRUG DEVELOPMENT

4.2.2.1 THE FINANCIAL STRUGGLES

Drug development, as agreed by all respondents, is expensive. One of them explained that it costs, "around €1-1,5 billion to develop a product and this depends on the requirements: it has to be safe, the studies must include a lot of clinical patients in order to prove the drug is harmless. The amount and size of studies have led to a long development time, around twelve years." Regarding the entrances that lead to medical breakthroughs, the really big ones come rarely. It is not easy and it puts a lot of pressure on the employees, several respondents agreed. One senior manager said: "and if you pull the rug from underneath our feet regarding small improvements, then we don't even have an inflow of money that could have paid these big breakthroughs." The biggest challenge for the company today was said to be that of being able to supply the market with the new drugs when the big patent expirations come in 2012, 2014, 2016. One professor said about the general situation: ***"We are in the middle of a crisis where the pipelines today are almost dry!"***

One researcher made comparisons with the car industry, stating that, "no one drives a Volvo PV today", the point here being that the drugs can stay in the business longer than other products such as cars. An example was given from year 1899, when Bayer, the German pharmaceutical company registered Aspirin, acetylsalicylic acid that is still used today and is "gaining more and more interest and value".

One respondent meant, "It isn't a philanthropic enterprise, at least not the private drug industry". New business models with new partners have to be found – "we have to find where it is economically manageable to develop new drugs, where the industry wants and dares to enter, perhaps the disease areas that haven't gained so much interest due to the small number of patients," the respondent continued. Other respondent's also mentioned the importance of finding new partners and the new disease areas as being future possibilities.

In order to be economically more effective, it was mentioned by several respondents that it is important to "kill" the substances early, to stop the projects in time, before they have gone too far – because the further one project goes the more expensive it becomes. But this might have consequences. One middle manager reasoned: "You do it because you don't dare to... You know how hard it is to get it approved, how much it costs… so it can well be that we have killed a lot of substances here that could have become something. But with the sector being so uncertain and no one willing to pay... you will instead stop the projects very early."

4.2.2.2 THE INTERNAL AND EXTERNAL REQUIREMENTS AND CHANGES

The satisfaction of the owners was described as the foundation for the continuing of the enterprise. One group manager also meant that if "the investors even to the slightest think that it won't pay off, they will go somewhere where they can get a better yield."

One scientist explained, "Up to one-two years back there was a very quantitative view on this, so the board of directors decided that within this time period we should launch so and so many new drugs. We /.../ measured the failures, how much of the projects that disappeared. From the human testing to the launch there is 90% that disappears. It is depressing, but so it is." Furthermore, it was explained how this led to the company having more "numerical" goals that they started each year, which resulted in having too many projects in proportion to what could be handled. That meant the enterprise "moving very slowly". Some years ago this philosophy changed "180 degrees". Now one could ***"forget the numbers game and concentrate on quality."*** Every time the company came to a milestone, they would decide whether to continue or not.

Regarding external changes, several researchers and managers mentioned that today there is a lot of talk about personalized health care. The patients are much more conscious and ask about which drugs are available for treatment, they want to decide more. Several respondents had a positive view on the patients having higher requirements. But one group manager said that it has also happened that a doctor prescribes an indication that isn't approved - also called off-label prescribing -, which might lead to serious consequences. However, the industry does not have control over this.

There are possibilities seen in the rare disease medications - there is more interest in the smaller disease areas that have fewer patients. It was mentioned that it might be easier to come forward there because less documentation is needed, compared to diabetes, Alzheimer or other central nerve system diseases. And also the possibility to charge high prices for these drugs is of importance because the prices and yield will make the investment worthwhile.

4.2.2.3 RISKY GAME IN A TOUGHER CLIMATE

This industry means high risks, several respondents meant. "Nine out of ten projects that seem promising in the beginning never become anything", one of them said. Another meant, "Out of the 100 projects, 3 will succeed". Yet another opinion was that "the whole sector is a risk, there are few other sectors where you have such risk built in the system". But the motivation is there – if one succeeds there is enormous yield.

The climate has also changed. One researcher explained, "I believe that long ago we might have started the projects more casually, but now we have more and more data... and of course if you have more data then you shouldn't really ignore it, so..." Additionally, one middle manager meant that the climate has become tougher but "of course we want to deliver (the goals)". There is a lot of pressure to find something new and in a way this could also prevent innovation, was another opinion from a senior manager.

"We are much more measured", one middle manager stated. There are more budget restrictions due to the company not having succeeded to develop a new drug for some years. Additionally, many mentioned patent expirations in 2012, 2014, of these drugs several were said to be well selling drugs. The sales can decrease rapidly due to the generics entering the market. A senior manager stated that "These tough times can also make it tough to be a manager and lead because we have worried employees and you have to support them more. So the times have become tougher."

There is another challenge mentioned by two middle managers: the financial crisis that results in many countries not being able to pay for the drugs. So on one hand the authorities do not want to approve NDAs and the countries cannot afford to pay. On the other hand it does cost a lot to develop a drug because the studies must be so big due to the authorities requiring it. One respondent concluded, "So… this is why it's so difficult in the pharmaceutical sector right now, it is tough times."

One former executive had an insightful opinion about the impact of blockbusters and explained how the term "blockbuster" came to use by the Alliance to spread terror among the German civilians during the Second World War. "It was a huge bomb with 500-1 000 kilogram of trinitrotoluene (TNT) - that was a blockbuster", and just as the name indicates, powerful enough to bust whole blocks of flats in the enemies' cities. Blockbusters are literally destroying the Big Pharma and definitely causing the end for this kind of platform. The respondent continued, ***"There is no pharmaceutical company that hasn't been harmed by a monumental success"*** and gave examples of Roche with Valium and Librium, Hoechst with Lasix, GlaxoSmithKline and AstraZeneca.

A blockbuster brings plenty of money to the owner at first, but after the patent expires it becomes a problem. The blockbuster - or the "cash cow" - will only generate a fraction of what it earlier delivered because other companies can produce the same drug and offer it for a lower price. If no substitute is found, such as a new blockbuster, heavy losses are about to occur due to the huge R&D structures raised with the blockbuster money – this is what the respondent meant is "destroying the Big Pharma". The respondent's conclusion was that the blockbuster model is unsustainable, and it is/will be the main reason of the problems in the pharmaceutical industry.

4.2.3 THE AUTHORITIES SET RULES OF THE GAME

The regulatory system plays a significant role according to respondents. In some views, a too big role, as the requirements are very high, and the guarantees that are given to the company are not satisfying enough. Earlier, the amount of patients tested in clinical trials could be 400, whereas today it is 30 000. Thus, the regulatory systems have received some criticism from some respondents. However, other respondents took a more passive role and meant that "it works well" or that "we can't change it".

Furthermore, examples were given about FDA, the tone-setting authority in the world. Vioxx lawsuit is brought as example of why the authorities became stricter (Authors' note: Vioxx was an arthritis drug developed by Merck & Co, approved 1999. It had side effects causing

heart attacks/cardiac deaths. The drug was recalled 2004; however the scandal around it grew very big, due to thousands of patients involved.). Also the catastrophe with thalidomide, (Neurosedyn in Sweden) is mentioned by several respondents as one of the big failures that occurred in the 60-s. That happened despite AstraZeneca having done everything properly regarding juridical and medical aspects. Reflecting over this, one manager said, "Sometimes it is important to put on different glasses". This experience has led to AstraZeneca valuing and focusing on ethics very high.

Today, big studies must be made where one has to show in a big population that a drug does not increase risks for cardiovascular event such as cardiac infarction and stroke. Such rules affect time in market that becomes shorter and shorter each year, because of the higher documentation requirements. "Within the industry, one might think, 'Let's make another study just to be sure'", one researcher stated. Regulatory authorities play a big role, and it can even kill the innovation because one becomes trapped in its own bureaucracy, one respondent said. But these are the rules of the game, some respondents meant.

Another shared opinion was that earlier it was popular to create drugs that only eased the symptoms such as lowering the blood pressure with certain mmHg which could be seen as an indirect treatment. Today the authorities want facts about the endpoint instead of surrogate endpoint. "No one says that you actually live longer if you have lower blood pressure, but nevertheless the study must show that anyway, you have to study the patients until their last days," a former executive gave an example.

It becomes harder to create something due to the many parameters to take into account, is the summary of opinions regarding the situation. In a big company that is over-bureaucratized, the studies become more expensive and it can cause the big companies to choose not to develop some drugs because the market is too small. Furthermore, different countries require different documentations (Japan, FDA, EMEA) and this leads to the question whether it is economically motivated. Half-ironically, one respondent stated, "You can make the pharmaceutical companies very profitable by closing all the research centers and just deal with patents and then perhaps the stakeholders become very happy. There are both shortsighted and longsighted owners."

However, there was also opinion that the companies themselves are making the development longer than needed - "Everyone has tried to rationalize their research /…/ to shorten the time of drug development with new technologies and superior documentation. Has anyone succeeded? No… the total time of development is almost the same!" said one former executive.

Some respondents meant that the regulations itself are not preventing the innovation. Still, it was said that today "There is no authority that accepts small improvements". Demanding big changes and radical innovations might prevent small innovations. Another respondent meant ***"it has become a harder puzzle for us"***. Some of the respondents also meant that it isn't only about the safe substances and to be able to test them in humans, but it is also about the drugs giving the expected effect.

One of the respondents said that perhaps there is a pendulum effect in this: "… perhaps it will be 20 years when it is difficult to get the drugs approved which leads to the decrease in the number of registered drugs, but in 20 years maybe there will be such a big medical need and then the authorities agree that 'we will have to approve more drugs because the patients are dying or do not feel well, because they are not cured'." The respondents also said it is time for the authorities to see the benefits and not only risks.

4.2.3.1 THE PATENT TIMES

Through to a patent one has 20 years of exclusivity, however this time was seen as too short, due to the tough competition and long development time. A patent must be filed quite early in order to "research in peace". One researcher meant that "If there is no patent space to work in, that you can have a patent on a product that you perhaps develop in 12 years then there is no point to work with that at all. Already when working we have to know that there is at least a chance to file a patent in this area." There are very big, costly studies with a lot of patients and the launch can delay a lot, from 6-12 years. Another one said, "Whether it is frightening or not... well it isn't, but it is still a remarkable perspective because we do not know whether the thing we deliver is good or not before 6 or 5 years have passed – and even then we cannot be sure."

Furthermore it was said that earlier when a drug came out there was more time to get the invested money back, but now it can take up to 15 years before a drug is launched, meaning the investment won't be returned. The patent times do not need to be longer, one middle manager said, but maybe if the patent time started to count from the time of entering the market, then this would make it worth focusing on.

4.2.3.2 THE PAYERS FACE FINANCIAL CRISIS

One of the respondents said, "there is nothing that stands a human closer than his own health, and then the humans will always be willing to pay for the drug." This is not the case right now, as due to the global recession the attitudes of the big politicians have changed and the countries with the least money are not willing to pay for new drugs. Shockingly the respondent even meant that the authorities sometimes do not accept the drug because they can't afford to reimburse it later, saying "we haven't approved any drug for several years because we cannot afford it". The payers see drugs as a cost rather than an investment, another respondent agreed. An example was given of when the company visited Eastern Europe, meeting the financial and prime ministers who had said something like "I know why you are here but you can just as well leave because we will not buy your new drugs as we cannot afford it." Another example was given about Greece that cannot afford the drugs at all which is a big emergency.

4.3 ORGANIZATION AND MANAGEMENT

4.3.1 THE ORGANIZATION

4.3.1.1 DOES THE SIZE MATTER?

Regarding the size of pharmaceutical organizations, respondents had different opinions. The old organization was described in positive terms, and seen as more flexible, thus making it possible for decision-making to be closer to the researchers, having less bureaucracy.

"Pure idea wise the big organizations are not meant to be so innovative," was an opinion from a former executive. "With large units it is hard with all this innovative stuff," a middle manager said. A professor stated, "Bureaucracy is time-consuming and makes the enthusiasm fade!" Several respondents meant that small units, business units that have a lot of external contacts are good. "The smaller format is always to prefer, it's the same as global versus local issues," one respondent stated. Central big organizations were seen as inert whereas smaller organizations would have advantages of being flat, making it easier for information to spread and the decision-making to occur. If an organization becomes too stabilized it might be effective yet not so creative. One researcher explained: "One cannot order innovations from above". A group manager stated, ***"We need faster, shorter decision routes... it is hard to maintain the flow with 60 000 employees. It is the biggest challenge today I would like to say. It's like with boats – if you sit in a little one you can turn around faster."*** "We have a lot of muscles but we could use it in some clever way, that small format that builds innovative and creative environment," another respondent mentioned. Furthermore, a group manager mentioned that this situation is further affected by the fact that there are too few researchers in the labs.

One researcher said that one is not required to be innovative in a big company; you don't have to worry about tomorrow. Another opinion was that a bigger organization might not be more innovative but it can do more. The small companies can maybe handle one project, but at AstraZeneca there might be maybe 500 projects. The big companies are created to take care of the ideas (as opposed to create ideas), they have the economical muscles. "Economy matters because of the simple reason that innovation takes time. You have to have endurance, the money to pay the rent, tools, and employees", one principal scientist said. Counting the innovations, the big companies will have a bigger amount than small ones, but measured per capita, per individual, the small ones have more innovations.

Regarding investing, a former executive meant that many venture capitalists are afraid to invest in small companies because these can be ruined fast. After all, a lot of money is required to find new drugs. "Maybe I'm exaggerating but you could compare one project at AstraZeneca to a small biotech company," was the respondent's opinion. "The projects come and go all the time in this early innovative phase. Every day one project the size of a biotech company is stopped, yet no one notices it because there are often more people engaged in the project here than there are employees at one (small) biotech company," he explained.

4.3.1.2 THE IMPACT OF GLOBALIZATION

Respondents have explained that today the organization is bigger and global. However, the opinion was not necessarily that the organization today is too big – but some respondents did indeed mean that in their eyes this is the case. The organization is now divided into different functions according to one respondent. This is not seen as a direct problem, but according to the respondents, it can make it difficult to communicate with different countries and cultures.

AstraZeneca has become a global corporation through the merge, which also meant becoming international. Furthermore, it was said that different cultures have different approach to

innovation, such as allowing thinking outside the box. A middle manager stated, "It can be hard if you don't always understand the different cultures. The language, ability to listen and understand what the science is telling you."

The globalization sets new requirements to effective communication. Infrastructure was mentioned as something basic yet very important today: "that the phones are working, that you can enter with the passing card, the Internet is working". One manager said, "With the help of internet, e-mail, mobile phones and WebEx meetings it feels as if the colleagues from the rest of the world were sitting here. But it is always an advantage to meet people in real life; the communication will be more effective." New types of communication could be used for many things, such as (hypothetically) using Facebook to find a patient group for a study. These possibilities are tried to put in use and improve, according to one respondent.

Globalization means opportunity to enter new markets and the medical needs are seen as consistently big. It was stressed by several of our respondents that they do not operate in isolation, but are part of something bigger, part of the society. Furthermore, it was mentioned that different regions in the world might require different medicines, or different approach to medical research. Thus, in order for the drugs to be used there are many studies needed on the respective populations. For example in Japan one has to take into account their different metabolism. The pharmaceutical industry is trying to design studies of products that can be used in the whole world. One respondent said that this is not yet possible today, not even with the big study populations and materials. Sometimes one has to build up a scientific base that the authorities can refer to – it is not about fooling anyone, but to create science around the product, a respondent meant – "It took 10 years to convince the medical world that asthma is an inflammatory disease and the corticosteroids, apart from the side effects, could be useful on the patient already from the first day."

4.3.1.3 LEADERSHIP AND DECISION MAKING

One of the managers explained that innovation is discussed very intensively in this industry. The leadership is very important for the drug innovation, meant another respondent – it can give both vision and also inspiration. According to one scientist, there is too much focus on negative deviations from the plans - what about positive deviations that could give something new? It is also a balance question of efficiency and creativity – to dare to take unexpected decisions. Furthermore, decision-making is very hard because there is a lot at stake, one manager meant. As a manager, it is important to be positive on the outlook of creativity, and also to be brave. The managers encourage employees to think on the increasing of efficiency and how to improve, for example shorten the lead times. It was also mentioned that at AstraZeneca an innovation tool is used, where people can anonymously leave suggestions. Besides that there are conversations with the employees, where one tries to see knowledge that employees could exchange with each other.

Since 2010 there is a new research strategy for the early-phase researchers who then have more freedom but also more responsibility. The scientists are encouraged to use time for their own research, so that the research could be driven from within researchers' own competencies. One scientist meant that in their group, everyone can affect the research and

say what they think. The leaders have some preferences and expectations, but are trying to give as much freedom as possible. On the other hand, the respondent also described how certain goals are set within certain time spans, and that there must be some "all-embracing goal" to work towards, an amount of substances has to be worked on. According to the respondent, middle managers work together to decide these goals. Furthermore, the daily situation can actually change fast, due to new information, which might mean that the project must be stopped. One unit manager cannot take this decision: instead there will be a committee consisting of section managers deciding that.

Another respondent meant, "Sometimes I want more mandate, it feels that we have to take into account the higher level all the time." Leadership problem is recognized as nothing new, yet still central. There is a paradox in the leaders' demands – one middle manager explained: "We speak of words like "innovative", "creativity", and you think "Okay, they want us to be all that, but at the same time everything has to go faster, we must become more effective and achieve everything with less money" and then it will not be so easy to be innovative."

Cultural differences can affect leadership, for example in Sweden, according to some respondents, one listens to the people on the lower levels. One respondent explained, "Working globally you don't always dare to say what you think… you have to go through your manager. This is not Swedish to think like this – we are not so careful with whether you are a top manager or a middle manager, you can talk with everyone. And it is okay to say what you think." One opinion was, "There is a big difference hierarchically. Many grasp this, those who have international managers; they say that it isn't easy sometimes. You just have to do as the manager says." Another respondent meant that this influences the internal climate and can influence innovation.

A former executive meant that the leaders must have knowledge to support the research:" you give the researcher free hands to test new hypotheses and limits, to have diversity and allow to question and doubt". The smaller units are believed to stay together, working informally, like within the academy and in small companies. One respondent meant that "in the "old" Astra, Draco in Lund, Upjohn in Uppsala, everyone knew each other and had an open mind about developing new drugs, and that's how they succeeded. It's a style of leadership to be allowing." Another respondent said that as a manager one can "set standards that other people can be proud to be associated with". To be a good example is also a way to achieve power and influence.

One researcher gave an explanation why Losec succeeded. The project of Losec was repeatedly proposed for closure due to many times it seemed to be unsuitable as a drug. The researchers did have the power to make the go/no-go decision at that time, but it was still very hard to decide. The management group was there for the researchers, but not to take part in the decision-making themselves, but instead to inhibit influences from outside of the research group. The management's main task was to let the research group make their decision without any form of disturbance and bad influence from outside – the managers were protecting the researchers.

Summarizing, a former executive said: ”Decisions must be taken close to the researchers, because then the decision makers will understand what they are deciding about.” Other opinions included that earlier the leadership was closer to the employees; it was a different culture, and that it was better back then. It was also stressed how the right educational background is crucial in this industry; several respondents meant that they benefit from their chemical education.

4.3.2 HOW TO PROMOTE INNOVATION

4.3.2.1 MAKING OF A CREATIVE ENVIRONMENT

In Genentech (USA), which is regarded by a group manager as one of the most innovative pharmaceutical companies in the world, every researcher can dedicate one weekday for their own research. “To be innovative is a cultural question, and this is hard to achieve… an environment where one is allowed to be curious,” he explained. One researcher added, “In the big companies you might be curious about “wrong things”, you don’t have to think to survive until the next day.” It was mentioned that there is a focus on the sidetracks that often do not lead anywhere but sometimes might lead to enormous discoveries. “The process thinking we have here has something of a disadvantage,” one respondent meant.

The climate has to be such where one can work and do mistakes. One director stated, “If you look at Nobel Prize winners then they often have had a lot of money to use, which means you can do mistakes. Then you dare to take risks.” But one researcher meant that Nobel Prize winners are always creative, they simply think of ways that no one else does.

One respondent said that there is more freedom in big companies, “You have the volume of resources around you; you can do much more than you want than in a small firm. Freedom means autonomy, to be self-directed which is very important, but of course it is followed by a responsibility all the time. It is very important that people can say what they think, to not limit but instead trust the employees.”

Lastly, there were opinions that “Today, there is a shortage of ideas rather than a shortage of capital” and “the big corporations do not have good environment for the early research and the search for new treatments. It is more suited to the academic environment and the small biotech companies where you work with one thing at a time. But the big companies are masters at taking those findings, to refine these to diamonds so that they can be produced and delivered out to the whole world.”

4.3.2.2. ENCOURAGING SELF-CONFIDENCE AND PROMOTING COOPERATION

It is very much about leadership – to celebrate the successes but to be alert for new and bigger ones. “You have to know a lot, willing to learn a lot, to be flexible and want to develop, but it is also about leadership where you encourage creativity, you reward it, recognize and give attention to it, give positive feedback,” one group manager meant.

Another respondent gave an example from the previous work group at Karolinska where their group leader had made a very big discovery in the 60’s, namely how to visualize the catecholamines in nerve cells. Basically all people from this group had become very successful and respected. The respondent pondered: “So the question is how it happens –

perhaps you think that the group with good reputation and success, they recruit only very capable coworkers, but /.../ there must be something more… I believe that it is about self-confidence, that in such groups you can build it up." The idea was developed further, ***"Each and every American thinks they can become a president of the country at some point, but here we limit ourselves too much.*** Sometimes I say, dope your coworkers or hypnotize them and make them believe that there are no obstacles, that they are the best and there isn't anything that they cannot do. And then they will perform fantastically!" the respondent explained. However this is not to be confused with isolating oneself from the external world and refusing to take criticism, the respondent meant: "it's about giving criticism in a good way but most importantly to receive criticism in a good way. To receive criticism as a gift because in best cases it is a gift."

Another respondent said that it is believed that single researchers contributed to big discoveries like Losec – but actually it's about having a team. "Once one discovers a molecule, other competencies are needed, perhaps hundreds of people - and this means complex networks," the respondent explained. Thus, the ability to develop a new drug depends on the individuals' ability to work together and share the knowledge. One respondent stated, "/…/ A group of competent people, it can work, but not necessarily. Think about how to put together a group. The self-directed groups, they move together and have ability to attract competence that is good or adds something to the group. Regardless the size of the company, a self-directed group is best. It can be formed and built in another way."

4.3.2.4 WHAT MOTIVATES THE RESEARCHERS?

One researcher explained: "Failures in reasonable extent are good because then you learn something from it. Sometimes you have to be lucky as well, to succeed. For me it is important to know what you want with what you're doing /…/ the time you are at wok you should focus on what you are doing and also think that it is fun. You have to feel this drive … because then you might also think "we have to think differently" and you have the goal in front of you all the time. This, I believe is very important, and we also talk a lot about this that in the end it is about the patient, this is why we exist." Curiosity is the best driver according to another researcher, but "when you can also earn some money with this, it's always good".

Among our respondents, the main ideas were that one has to have innovative mindset and also feed the innovative work. One group manager mentioned there is a paradox: "On one hand you can feel quite framed to what you can do, but on the other side people admire researchers who don't give a damn about the system, and do what they want. For example, two researchers who left the building long ago /…/ ***They were the "dark horses" who didn't give a damn about any orders, they did what they wanted - you can only have one such person in the organization. More would create chaos, complete chaos, it's like a conflict there, but you really need such people."***

There are bigger motivations in self-directed groups - they are after something more than payment, the desire to participate in something bigger, one researcher meant. The bonus

systems can work well in other companies, but it is harder to motivate the scientists, for them it is the free thinking that is most important. A former executive said that sometimes the misery is the mother of innovation - when there is a real crisis then people are "damn good" at discovering things.

4.3.3 COOPERATION OR COMPETITION?

One senior manager said that there is only one employer in Gothenburg, AstraZeneca, so it could help to have "more friends" in this geographical region: it would contribute to the "pulse" of the industry. Astra Zeneca is "too lonely" right now, meaning that people are limited to only one workspace. More competitors would improve innovation and research culture, the respondent stated.

One group manager said, "My colleagues in the academy do not understand how much knowledge and experience here is /…/ There is a lot that is not marketed or published, and I believe that more openness would benefit us a lot. ***Right now there is fear to share something you see as your property. Of course, one has to be careful, but I think the cooperation would promote the innovation a lot.***"

Other opinions were that competition stimulates work. Often the companies check on each other and know very well where the others are regarding their research. Sometimes one might leave the area of research if the competition is too high. The competitors can thus challenge and contribute to better innovations. "There is an intrinsic joy in being able to create something new," one respondent meant.

4.3.3.1 COMPETITION

To prevent competitors to develop and sell the same drug, patent system is used. Regarding as to how the patent filing works, it was mentioned by several respondents that they want to apply for patent as late as possible, to be able to use the time maximally. It would be very demotivating, one respondent meant, if the competitors should find out and "steal" some project.

It is a race, absolutely, one middle manager said. "There is a term fast followers, I don't think it is something bad; likewise it might trigger you more. But the information has become much more exposed the last years, because you are required to publish the information about the studies you do. It is for the patients' sake, not for the pharmaceutical companies to know what the competitors are doing. So it is not such a secret compared to before."

Sometimes one can also learn from others – "We learned a lot in another project how to optimize or improve a series that others had published. We work on it and think that in the beginning we can find something much better than what they have produced," one respondent stated.

4.3.3.2 COLLABORATIONS

But collaborations are possible, as well. Often the competitors have other areas of research, but perhaps with technologies that one would be interested of. Sometimes the companies can work together, for example to solve the waste problems. One respondent stated that external

collaborations are not so rare, "Today we have thousands of collaborations, 40% of the whole research budget which is USD4,5 billion, is outside the company. We seek cooperation with the best ones in the whole world."

One group manager meant, "I would gather all the pharmaceutical managers and say that "we all are in the same shit, fighting with similar problems… we benefit more from cooperating than from competing in an early phase /.../ I guess it's better that everyone comes up to the course and starts running and competing rather than no one starting at all." There are initiatives like different consorts between pharmaceutical companies. Hazardous waste was mentioned as a big problem that often occurs late, when one has invested in the project in years. To fix this, a shared database was created, of chemical structures associated with different toxins. Another example is Innovative Medicines Initiative (IMI) that was described as "precompetitive". (Authors' note: IMI is an EU project to maintain competitiveness in Europe, as USA and Asia are emerging.)

4.3.3.3 THE VALUE OF PRIVATE PUBLIC PARTNERSHIP (PPP)

When it comes to PPP, many of the respondents agreed that university has played a big role: "We would not be here in this region if it wasn't for the university", "it was a strategic decision to move to the regions with big universities". The universities and pharmaceutical industry can complete and learn from each other, because the former is more explorative and the latter is focused on product development. The site in Mölndal was created due both the hospital getting university hospital status, and the pharmacy institution at the GU being very successful. "One has much to win from the cooperation with researcher groups, who have different mindset," one respondent reasoned.

However, the opinions differed regarding today's situation. Some meant that the cooperation is very important today as well, and that the university can give more innovative environments. Others meant that due to globalization, the academy might not be the first choice for cooperation. Furthermore, it was mentioned that there occurred a situation in the 90-s and in beginning of 2000 when the university engaged in entrepreneurial activities and both the industry and academy distanced themselves from each other. The reasons for that were, according to one respondent that the universities wanted to protect their identity and also market themselves so they shut themselves.

It was said that the collaboration between university and academy could be tighter, but there can be a conflict of interests, or more clearly, it is difficult to satisfy both parts. However it does not work to be so distanced from each other, it costs too much, was another opinion. "We create these collaborations because we believe that we can get something out of this, and also the universities get something, like the finances for their research," one respondent explained.

One group manager spoke about the cooperation ability: "Aspects like that are to our (AstraZeneca's) advantage because here the individual is important, but it is still the group that matters. You have to have a common goal /…/ you don't have the harmful competition that you have within the universities. It gives people opportunity to be generous – they share

their knowledge in a different way, which is good for innovation and creativity." Another opinion was about recruiting new researchers - one respondent said that if the researchers would come directly from university and hoped to create new drugs, they would run into the wall fast. "They won't understand what is required to develop a drug like the authorities require. They can publish very exciting data but it is completely irrelevant," the respondent stated.

4.4 THE FUTURE

4.4.1. THE INCREASING MEDICAL NEED

Regarding the future, most respondents mentioned the increasing medical need. One middle manager had heard that children born 2011 have already life expectancy of 100 years; the chances of getting so old are that good. Even though older people are healthier today compared to before, the big number of them is believed to cause this need.

In India and China there are big possibilities created by the emerging middle class. One middle manager explained: "It gives them chance to buy drugs... so I think that there might still be space for us in this industry. I think that the future is bright even if it might look a little bit dark now." A group manager expressed the medical needs with following words: "If you think about it, then at the end of the day it's only about the human beings". The pressure from outside was said to be huge – ***"Everybody wants to live longer and be a teenager up to 70 years age, play golf and be sexually active",*** meant one senior manager. "Alzheimer is one of those "clear as a bell" examples /…/ ***What if you could give them 20-30 more years when they can still be members in their Rotary clubs, socialize with grandchildren and contribute to the society?"*** he continued. Alzheimer and obesity medicines would make a big difference for the people and the society, according to several respondents.

4.4.2 THE MATURING TECHNOLOGY AND SUPPLYING THE COMPETENCE

One middle manager stated, "There are a lot of (natural) scientists here, biologists, zoologists, doctors, nurses /.../ Maybe we need to mix them with some IT people, technically capable people. I can feel that sometimes we are a bit in a stone age when it comes to IT." Supplying the competence was seen by some as a big challenge. There are not many people who choose long educations like Ph.D., one respondent said. In the long run, the low interest for the natural sciences is also a threat - one respondent gave an example that in Sweden right now only four people are studying to become a chemistry teacher.

Regarding technology, one group manager stated: "/…/ in the beginning one is very enthusiastic, but then starts to see both advantages and disadvantages. I believe that the innovation within the industry might increase because many of these techniques will mature; one will understand them better and can use it more effectively /…/ When HTS came then it was very much cheering for it and we could suddenly screen hundreds of thousands substances. But the HTS didn't give so much, and today you start to see the results, you get more sober view on HTS technology, due to the molecules discovered with HTS technology that entered the market."

The same was said about genetic research and projects around genome-wide association (Authors' note: it is a study to examine genetic variants in different individuals), which have not met the expectations one had. A group manager meant, "Today we try to understand heterogeneity of the patients; there is a lot of talk about personalized health care." It was also mentioned that the intelligent drugs will increase in the future, e.g. by using nanotechnology.

Translational science was mentioned by several respondents as reducing risk, helping to identify successful projects earlier. One principal scientist meant, "There is a bigger challenge in being able to simulate, reflect and understand the early preclinical results. To counter the patent times, it could be a solution to offer the patients/clients complementary service, something that makes them buy this original medicine even after a generic has made entrance to markets." A senior manager agreed, saying, "It is about more than just producing a bottle of pills"

4.4.3 INNOVATIONS ARISE FROM SMALLER GROUPS

One researcher meant that an innovative company who wants to reduce the risks will have a burden of high development costs, compared to a sales company. But the latter will not survive in the long sight, so the paradox is that one must both develop and at the same time have good sales. "/…/ people believe this can be solved through a merge, but this has not been the case. The big ones sell better but do not have so good development. So I think we are moving to the situation where the creative ideas will come from small research groups who then sell their ideas to big companies that can develop them," the respondent continued. One professor agreed, saying, "Fusions have showed to be a flop, it is not an offensive strategy but the opposite – a defensive strategy".

The big companies are said to be too big to be cost effective, one researcher explained. There might be a breaking point where one won't get any new products so that the research can't be financed and there won't be any cash flow. A former executive compared the situation of Big Pharma with the extinction of the dinosaurs. Further, he stated that "They cannot meet the shareholders requirement for profitability development. At the bottom this is caused by their inability to solve the supply of new products."

Regarding externalization, one senior manager gave an example of Encubator in Gothenburg. Others can use the ideas and projects that the company itself found not profitable enough for them. The smaller companies do not have this capacity themselves, to do all the tests, so that's why they sell "half fabricates" to big companies. Even though active cooperation is always needed, the question is how externalized can one pharmaceutical company become, one researcher meant. The big organizations will still be important for the process. Another researcher said that the big companies are already buying ideas that have passed pre-clinical phase, from smaller ones, to then execute these.

Organizational creativity and innovation is always directed, another respondent meant. But there are possibilities to look beyond these frames and business models, such as Apple has done with iPhone. It will be more than just producing the product. ***"Keep big ones lean. Create the small units that have clear mandates. Smaller groups, business***

units, create those smaller boats that can turn around more easily," was the advice given.

4.4.4 THE PARADIGM SHIFT

Regarding future, the respondents agreed about the need for smaller organization size. Both smaller unit sizes with more responsibility and autonomy, and completely reformed, smaller research organizations were named as possibilities.

The early research will come from the university, some meant. A former executive gave an example: "There are 15-16 000 employees in cancer research /…/ having billions of dollars to spend. The pharmacy industry does not have top competency, the universities do. But still the industry spends billions of dollars straight out, it's completely devastating and will certainly change." One professor compared the amount of money the industry possesses versus the research budget of the universities as "a Manhattan skyscraper versus a wood hut".

The future is exciting, several respondents agreed. The knowledge around diseases has never been so high as today, it's about using the knowledge in a good way, one group manager said. It was seen as important to create an environment rather than a formal organization and to let the required competencies unite. ***"The pharmaceutical industry stands before a paradigm shift; I believe one will start more and more collaborations with the external institutions, decreasing their own bureaucratic structure,"*** one respondent explained.

5 ANALYSIS

5.1 PROBLEMS AROUND THE DEFINITION OF AN INNOVATION

There are variations in the very definition of innovation itself, both in the theoretical framework and among our respondents. Conclusively, the general understanding of innovation in the pharmaceutical sector is that it is a pharmaceutical product that meets some kind of medical need. Some respondents tied innovation to benefitting society; others were more focused on the truly new drug discoveries. Some respondents mentioned first-in-class pharmaceuticals, filtering out 'me-too', whereas others believed that the whole complex process of drug development is an innovation. But the respondents agree that pharmaceutical innovations are different from other innovations; it takes long time to develop new drugs, and the development is tied to high costs, big risks and uncertainty.

The data from interviews demonstrates that pharmaceutical innovations can be categorized as an innovation according to the definitions mentioned in theory. Even the diversity of definitions among the responders corresponds well to the theoretical spread of innovation definitions, such as Trott's idea of innovation being a process (Trott, 2012). Additionally, for a researcher the innovation might be tied to their specific area of expertise, but for a manager innovation might mean something more widespread. However, the variation in this case is **not** explained with respondents' different occupations. We believe that the variation might

increase with larger study; however the general understanding of innovation remains the same throughout the whole industry.

When answering the question about what an innovation is, most respondents chose to exemplify, often mentioning Losec. Despite the struggles, it was well accepted by the market and brought a fortune to the company as their most sold drug on the market. This indicates that innovations in the pharmaceutical industry could be ranked - some innovations are better than others.

5.2 THE COMPLEXITY OF PHARMACEUTICAL ORGANIZATIONS

5.2.1 TECHNOLOGY PUSH OR MARKET PULL?

Trott (2012) writes that in order to study innovation management, one should include other areas to get the big picture. After conducting the empirical study, it is clear that this is indeed the case and that one cannot study innovation management completely isolated from other areas.

Additionally, Trott (2012) means that the innovation in the pharmaceutical industry is caused by a technology push, rather than market-pull factors. However, in this study respondents spoke of both. Technology push examples are HTS, translational science, nanotechnology and genome associations. But many respondents said that the medical need - the market demand – is also important for innovation. Diseases such as cancer and Alzheimer express a market need where technology hasn't yet been able to solve the problem. Furthermore, good innovations are described by many respondents as being radical and contributing to the society by curing diseases that one hasn't been able to cure before. Lastly, technology is not always viewed as something positive, as is the example with HTS, which has received criticism from some respondents as being ineffective. This discovery problem with HTS is also supported by an article from the journal Nature Review (Swinney and Anthony, 2011). Conclusively, market pull seems to affect the innovations in this industry at least as much as technology push.

5.2.2 INNOVATION IN ORGANIZATIONS

According to Burns and Stalker, today's innovations are created by people who are employed at organizations such as companies or academic institutions. Both Trott and Burns and Stalker mean that since innovations are made faster and faster, which sets pressure on the companies (Burns and Stalker, 1994, Trott, 2012). Also our respondents meant that there are more requirements and more pressure on the employees, and that the R&D is much more costly. AstraZeneca has tried to support the R&D and to encourage innovation, by giving more freedom for the researchers, to have more allowing leadership style and encouraging everyone to participate – the big general innovational goals should be shared by all employees.

When speaking about risk, it is clear from the interviews that innovation in pharmaceutical industry implies a big operational and financial risk – because of the regulation requirements, it is hard to guarantee if and when the drug may be accepted, and furthermore because of the patent system, it might be hard to get a satisfying return of investment in many of the cases.

Regarding risk, Burns and Stalker mean that risk-taking is necessary in the changing environments where the risk of change will be weighed against the risk of not changing anything. The status quo can have worse consequences and threaten the survival of organization (Burns and Stalker, 1994). However, in this case, our respondents stated that risk is hard to avoid since it is built in the nature of industry. Some mention the importance of reducing risks, effectiveness and saving money being the primary reasons for this. However, others have views of risk-taking being something to encourage, promote and test the individual researchers' abilities; trying new things is seen as crucial in order to make radical findings.

5.2.3 INNOVATIVE OR COMPLEX ORGANIZATION?

The multi-divisional companies (such as AZ) are said to have the benefit of diversifying their products, however in this case we do not see this benefit, because today's business model seems to promote blockbuster development, that because of the profits, the return of investment, and to cover the high R&D costs. Diversification - having a market share in different disease areas is perhaps not profitable and thus of smaller interest, and neither is it very realistic, given that the really successful drugs are only few.

Tidd also mentions that multidivisional structure can prevent the appearance of new competencies, making these companies to deepen rather than broaden their capabilities (Tidd, 2001). This is definitely important in the pharmaceutical industry, because it is apparent that new competencies, new radical findings are crucial for the survival, not only for AstraZeneca but for the whole industry. Deepening, but not broadening ones capabilities might not be sufficient, because the respondents have said that the innovations with marginal improvements are not really desirable. Of course, if the drugs generate satisfying income, they would be welcomed nevertheless. With the example of AstraZeneca we conclude that in this industry one must both deepen and broaden the capabilities.

According to Tidd, the pharmaceutical companies classify as "innovative", meaning that the uncertainty is high and the complexity low. By uncertainty in this case we mean the difficulties with predicting the outcome of pharmaceutical R&D, and by complexity we mean the difficulties to grasp the innovation process. On one side trying to manage the organization with huge number of employees and on the other hand managing R&D, like with the big clinical studies and documentation.

But during the time when the pharmaceutical industry grew economically and became today's Big Pharma, life sciences had become more complex. To deal with the strict game rules, the pharmaceutical companies had to be more bureaucratic which can cause a side effect of rigidity and hierarchical organizational structures. Researchers might have been affected as their power decreases and (too) many projects are started in order to counter the high failure rate. Furthermore, the bonds with universities seemed to grow weaker. This might have created a vicious circle that the pharmaceutical industry tries to break today.

From the collected empirical data it is clear that there is a lot of uncertainty, and that the complexity of the AstraZeneca and the drug development is very high. All of our respondents

have mentioned how hard the innovation process is, and they have also mentioned that the big organization is more hierarchic, more bureaucratic, slower, resistant to change and harder to lead. No respondent has claimed the opposite - that the organization as it is today, is simple, flat or easy to manage. However, there were opinions about big organizations actually giving more freedom, and promoting better teamwork than for example academies.

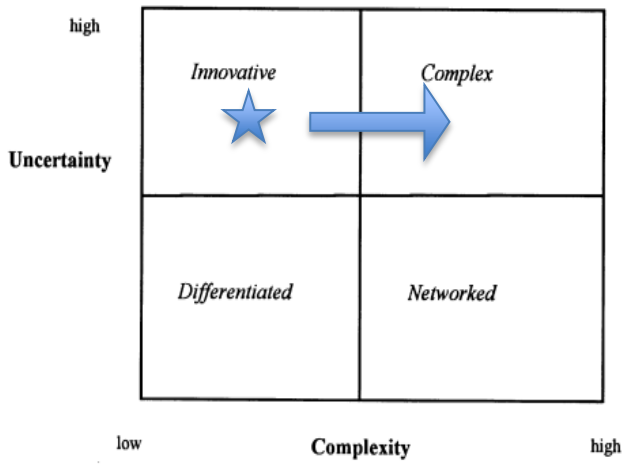

Figure 9. Effect of uncertainty and complexity on the management of innovation (Adapted from Tidd, 2001)

Looking at the four quadrants of uncertainty and complexity, we would place AstraZeneca in the "complex quadrant", see Figure 9. This can provide a partial understanding as to why the company struggles with successful innovations: perhaps it is supposed to be in the innovative quadrant, but it has "moved" over to the quadrant where it does not "belong".

This is supported by Tidd's theory of innovative organizations being more flexible and rapid to adapt and learn. Conclusively, the fit between the nature of the industry and the "ideal" organizational structure seems to be weak, which could affect the organization's performance. So perhaps AstraZeneca is trying to move back to the "innovative" quadrant. Through smaller units and more external collaboration, the company might try to build up an organizational culture and environment similar to the "good old times".

5.2.4. THE DEGREE AND TYPE OF INNOVATIONS

Furthermore, Tidd mentions the difference between types and degrees of innovations, meaning that one must separate radical and incremental innovations, and also process or product innovations (Tidd, 2001). We conclude that the Big Pharma and the small biotech companies are diverting into different directions of specialization, see Figure 10.

Many respondents meant that radical innovations in the pharmaceutical industry will come from the smaller companies or academy. But here it is important to explain what one means by "radical innovation". In this case it would be the early research, learning processes in order to find a new mechanism of action and also a substance. By contrast, the larger units or organizations are experts on the "product making", registration and marketing in accordance with regulatory requirements. (That is done regardless whether the innovation is incremental, radical or disruptive, so in a way the big organizations still help to make the radical innovations happen). It was also mentioned that perhaps AstraZeneca (and why not others?) can offer complementary services besides just selling the drug. Lastly, respondents indicate this change as the paradigm shift that is predicted in the pharmaceutical sector.

Some respondents mean that innovating in the pharmaceutical industry was easier back in history. Target diseases were less sophisticated compared to the advanced pathophysiology in e.g. Alzheimer and complicated syndromes e.g. obesity. For example, in the case of Losec, there is one target receptor and one mechanism of action. The different attitudes of regulatory authorities might also have been of advantage for the innovative climate, compared to today's situation with stricter regulation and tightening-up economic condition.

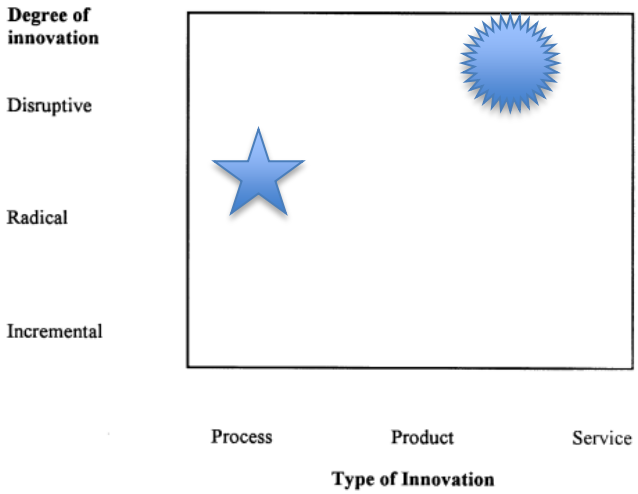

Figure 10. The degree and types of innovation. The star marks small biotech companies while the sun marks the Big Pharma.

5.3 MANAGING AND COUNTERING THE PROBLEMS

5.3.1 SEEING THE PROBLEMS THROUGH CORE CAPABILITIES AND RIGIDITIES

Leonard-Barton defines the core capabilities to be a knowledge set that distinguishes and provides a competitive advantage. There are four dimensions of core capabilities – technical system, skills and knowledge, management system, values system. AstraZeneca's core capabilities come, according to our analysis mostly from the skills and knowledge and their values system. The technical system and management system have potentially less effect in forming the core capabilities, because the company has gone through a merge which have probably changed both of these systems. Furthermore, the international nature of AstraZeneca can even affect the values system, as we believe we have found proof for in the interviews.

It is clear that there are rigidities emerging from the corporation's core abilities, and we have received several examples from the respondents, the rigidities emerging from the technical systems such as documentation systems and requirements. It seems also that the small companies have an advantage in the form of flat organization and faster communication and decision-making. However, the big companies have at some point been small themselves. This raises the question whether there is a breaking point where a small company must change, or choose to change; perhaps because they want to become more than just the "small radical innovators", maybe they want to be able to produce a drug and not just research?

However, the situation is far from status quo. It is important to point out that AstraZeneca seems to be working towards change, trying to cope with the rigidities. Respondents stress the need for smaller units and different business models and at the same time the courage and freedom to think differently.

5.3.2. SOLUTIONS AND FUTURE EXPECTATIONS

Many of our respondents focused on the importance of organizational learning, yet also stressing the importance of breaking it down to individual level. This could be seen as to making sure that everyone really is "with us". Even though we did not include any theory

about organization learning, this could well be very relevant. For example, Stata means that the key to innovation management is the ability of organizational learning (Stata, 1989).

Even if there is a problem today, some respondents explained that today's system is set for the future, whatever it will be like. The knowledge in this area is higher than ever in history and respondents imply that changes in the pharmaceutical sector occur naturally. One respondent forecasted the next 15 years of worsening in the business, but thereafter it would get better. This, we see, could match very well with Hannan and Freeman's theory about population ecology. With other words, the occurring changes are only natural, and an organization has to adapt to the situation in order to survive. Furthermore, that it might be hard to affect the outcome of a changing environment - it has nothing to do with the skills, knowledge or strategy, but simply the organization best fit for the situation will survive (succeed).

6 CONCLUSIONS AND CONTRIBUTIONS

The studied organization is big and complex, divided in different functions and sites with specific skills and tasks. This might affect the employees who are part of different functions or parts of the same organization. Seeing an innovation from many viewpoints can cause disunity and problem in the company's innovation management, according to Tidd & Bessant (2005). However, it's not known how this will affect the organization and innovations in the pharmaceutical industry, but we see this as a potential subject for a follow-up study.

It can well be that different pharmaceutical companies have different organizational cultures and approaches to innovations. Of our 13 respondents, 12 have been or still are connected to the same organization within the pharmaceutical industry, which might limit the possibilities for generalization. However, many respondents stressed during the interviews that the situation is probably same for other companies, as well. It could be another idea for further studies, to increase the amount of companies involved in the study.

The analysis shows several steps that AstraZeneca takes or is trying to take, in order to reduce bureaucracy and encourage new ideas, thus making way for innovations. However, the questions remain, how much can an organization change, are they changing into a right direction - is this actually a solution? This remains to see.

Perhaps the most important finding from the empirical data is not to be tied to any theory. In more or less every respondent's answers this was apparent that something big is happening or might happen in the near future, regarding pharmaceutical industry. Some respondents seemed worried about it; some were taking it more calmly, some being optimistic about it. Some were perhaps hoping for the change to happen, others hoping it wouldn't. This leads to the conclusion that there might indeed be a paradigm shift approaching and according to the theories it might be needed at this point. After all, several indicators point to the weak or

ineffective sides of the current pharmaceutical industry. This idea of change in this study is also what articles in the subject have described and supported (Hedner, 2012, Garnier, 2008).

We conclude that the solution to what we have described as the Big Pharma problem seems to come from something larger and big-scaled, perhaps a significant organizational change. Thus, the suggestion for continuing research would be to go even deeper about these specific problems in the pharmaceutical industry, but also to investigate this organizational change, and try to come up with possible future scenarios to better adapt to paradigm shift. With that said there are of course already several future scenarios named but there is space for more research in this area and definitely space for improvement, providing a deeper understanding. The interest to this topic is very big, which was reflected on the high response rate of this study.

Focusing on local situation (Sweden), the organizational culture in the Swedish pharmaceutical industry could be studied in further research project to better understand today's "dry pipelines" in Sweden. After all, this study was conducted in Sweden, and our respondents all being Swedish, it might be reasonable to continue the research in this country. Furthermore, some voices are calling for bigger investments in the Swedish medical research, so we believe this topic is of interest to several individuals and organizations. (Carlsson, 2012)

The metaphor "The extinction of the dinosaurs" was one respondent's comparison of today's changes occurring in the Big Pharma. Both these creatures and the big organizations seem to be big, rigid and obsolete, and the blockbuster can thus strike the industry similarly to the events that are believed to have caused the end of the dinosaurs. However, there might be a way for the industry to survive; perhaps the pharmaceutical "dinosaurs" will adapt to fast flying birds that can carry radical pharmaceutical innovations to the market. The radical ideas may be discovered in smaller groups but later speedily developed by the transformed pharmaceutical industry to become approved drugs.

The overall findings of the study were somewhat unexpected and as the authors of this thesis we react to these as being dramatic and critical, and more fundamental than we had thought. Mostly, because it seems near impossible to tackle the problem, or even to know how exactly to solve it. Therefore this metaphor, "the death of the dinosaurs", inspires to the title of this work – it gives a hint of the probable paradigm shift in the pharmaceutical industry. This comprehensive conclusion supports the dissertation work in the same scientific field from Sahlgrenska Academy at University of Gothenburg (Hedner, 2012).

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APPENDIX

Note: the original checklist was in Swedish

Name: _____ Date of birth: _____

Position: _____

1. **Introduction**
   - Personal Background
   - Education
   - Sector
   - Experience
2. **Organization**
   - Structure/bureaucracy
   - Culture
   - Coworkers
   - Trust
   - Knowledge
   - Decision-making
3. **Success**
   - Innovation
   - Measuring
4. **Innovation and difficulties**
   - Need
   - Requirements
   - Importance of randomness
   - Difficulties/Challenges
   - Possibilities
   - Decision-making
   - Product life cycle
   - Risks
   - Measure?
   - Competitors
   - Regulatory systems
   - Time to market
   - Time in market
   - The public sector
   - Failures
   - Time
   - R&D
5. **Future**
   - Increasing/decreasing? Why?
   - Innovation heights
   - Advice