Pharmaceutical Opportunities: A three-step repositioning model for evaluating market options

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Farmaceutiska möjligheter

En tre-stegs repositioneringsmodell för utvärdering av marknadsalternativ

av

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Abstract

Pharmaceutical industry is today struggling with its productivity as products keep failing after long and expensive development programs. The profitability is further threatened by fierce competition from cheaper product copies. As an attempt to increase the pipeline output, pharmaceutical companies have lately turned to the strategy of drug repositioning. By applying an already developed drug in new disease areas the lifetime of the product is prolonged and return time on already made investments elongated. Such development is imbued by less risk than a *de novo* development and has proven to be a faster and cheaper way to meet the medical demand.

With limited company budgets and the often many repositioning possibilities, an informed repositioning selection must be made. As such theoretical model is not publicly available this thesis takes on the task to determine which parameters to take into consideration and how these should be weighted in relation to each other in order to evaluate different drug repositioning possibilities. Six main topics are identified to affect the repositioning success, these are: *medical need*, *economic return*, *scientific support*, *timing*, *life cycle extenders* and *external relations*. These findings are derived from empirics collected during interviews with employees from five different competence areas involved in repositioning initiatives, namely: *research & development*, *clinical studies*, *regulatory affairs*, *pricing*, and *commercial*. By further support from literature within the fields of drug repositioning and R&D project selection a three-step repositioning model was developed.

The first step in the three-step repositioning model consists of primary parameters, these are essential parameters that have to be fulfilled in order to perform a repositioning strategy. If any of the primary parameters are not fulfilled, the repositioning opportunity should be killed in a go/no-go decision. In a second step, the secondary parameters are evaluated in a scoring model in order to determine the economical outlook of each repositioning opportunity. The opportunities showing greatest economical outlook should further be evaluated in the third and final step in the three-step repositioning model. In this final step the different repositioning opportunities are evaluated by their coherence with an overall corporate strategy.

By applying this repositioning model to a repositioning selection scarce company resources may be focused on the repositioning opportunities showing best future prospect. Evaluating the potential of repositioning opportunities in a structured way should also increase chances to succeed. If successful, a repositioning initiative may affect both company and society as the company improves return on earlier investments, while more patients in need of treatment will receive access to it. However, the three-step repositioning model presented in this thesis should be tested for more cases and perhaps be complemented with additional parameters or different gradings in order to optimize the selection.

Keywords: Repositioning, Repurposing, Life Cycle Management, Orphan Drugs, Pharmaceutical Industry, Selection Methods.

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Sammanfattning

Läkemedelsindustrin kämpar idag med en låg produktivitet som grundas i fallerande produkter efter långa och dyra utvecklingsprogram. Lönsamheten hotas ytterligare av den tuffa konkurrensen från billigare produktkopior. I ett försök att öka sin produktivitet har läkemedelsföretag under de senare åren vänt sig till repositioneringstrategier. Genom att applicera redan utvecklade läkemedel i nya sjukdomsområden kommer produktens livslängd att förlängs och avkastningstiden på redan gjorda investeringar kommer att förlängas. En sådan produktutveckling är mindre riskfylld än en *de novo*-utveckling och har visat sig vara ett snabbare och billigare sätt att tillfredställa marknadens medicinska behov.

I en situation med begränsade budgetar och ett flertal repositioneringsmöjligheter är det viktigt att ta välinformerade beslut. En sådan teoretisk beslutsmodell saknas i den tillgängliga repositioneringslitteraturen, varmed denna masteruppsats ämnar att utreda vilka parametrar som bör tas i beaktande samt hur dessa parametrar bör värderas i förhållande till varandra för att utvärdera olika repositioneringsmöjligheter. Sex huvudämnen identifieras, dessa är: *medicinskt behov*, *ekonomisk avkastning*, *vetenskapligt stöd*, *tidpunkten*, *livscykelförlängare* och *externa sammarbeten*. Dessa ämnen härrör från empiri som samlats in under intervjuer med medarbetare från fem olika kompetensområden, nämligen: *forskning & utveckling* (FoU), *kliniska studier*, *regulatoriska frågor*, *prissättning* och *kommersiella initiativ*. Genom ytterligare stöd från litteratur inom läkemedelsrepositionering och FoU-projektselektering kunde en trestegs repositioneringsmodell utvecklas.

Det första steget i trestegsmodellen består av de primära parametrarna, dessa är parametrar som måste vara uppfyllda för att en repositionering ska kunna utföras. Om någon av de primära parametrarna inte uppfylls bör repositioneringsförslaget läggas ner efter ett go/no-go beslut. I ett andra steg, utvärderas de sekundära parametrarna i en poängmodell för att uppskatta de ekonomiska utsikterna av varje repositioneringsmöjlighet. Möjligheterna som visar störst ekonomisk utsikt bör tas vidare till det tredje och sista steget i trestegsmodellen. I detta steg bedöms de olika repositioneringmöjligheterna efter deras samstämmighet med den övergripande företagsstrategin.

Genom att tillämpa denna repositioneringsmodell inför ett repositioneringsbeslut kan de knappa företagsresurserna deligeras till den repositioneringsmöjlighet som visar bäst framtida potential. Att utvärdera potentialen för repositioneringsmöjligheter på ett strukturerat sätt bör också öka chanserna att lyckas. Om det lyckas, kan ett repositioneringsinitiativ påverka både företaget och samhället. Som företag förbättras avkastningen på tidigare investeringar, för samhället kommer fler patienter få tillgång till behandlingen. Den presenterade trestegsmodellen bör testas på fler repositioneringsfall och eventuellt kompletteras med ytterligare parametrar eller andra graderingar för att optimera valet.

Sökord: Repositionering, Återanvändning, Livscykelhantering, Särläkemedel, Läkemedelsindustri, Urvalsmetoder

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Thank you all for making this happen!

Stockholm, June 2016
Sara Sandman

Abbreviations

ADME	Absorption, Distribution, Metabolism, and Excretion
AHP	Analytical Hierarchy Process
EMA	European Medicines Agency
EMENAR	Europe Middle-East Europe North Africa Russia
FDA	Food and Drug Administration
FoU	Forskning och Utveckling
HEOR	Health Economics Outcomes Research
IIS	Investigator Initiated Studies
IV	Intravenous
LCM	Life Cycle Management
PK	Pharmacokinetics
R&D	Research and Development
SC	Subcutaneous

Contents

List of Figures

List of Tables

Chapter 1

Introduction

This master thesis explores the phenomenon of repositioning in pharmaceutical industry, how to detect and evaluate market opportunities. By studying an ongoing repositioning process at a middle-sized pharmaceutical company, this thesis will provide insights from a real-life case. To start, this chapter will provide a background to this research project, present the purpose and research questions, as well as delimitations. The chapter ends with a disposition of the report.

1.1 Background

Pharmaceutical industry has been struggling for years to provide innovative drugs at reasonable prices, in order to address unmet medical needs. This has not been easy due to long and expensive development processes imbued by risks and strict, constantly changing regulations. Furthermore, the threat of generics and biosimilars (cheaper copies of drugs) has increased. These products enter the market at time of patent expiration, minimizing the profitability among the pharmaceutical developers. Finding innovative, fast and cheap ways of getting products through the pipeline to market has therefore become a key challenge for companies in order to survive in this industry (Ekins and Williams, 2011).

There are several strategies used to increase the pipeline output. One is to identify failures early on in the process, to reduce risk and cost of developing drugs deemed to failure (Buonansegna et al., 2014). Another strategy is to address inefficiencies in the conduction of clinical trials (Rawlins, 2004). Furthermore, companies try to fill pipelines through mergers or acquisitions. However, one strategy that lately has increased in popularity is the option of utilizing already branded products to increase the return on made investments (Barratt and Frail, 2012).

In order to prolong the lifetime of already existing products one can use several different strategies with long-, medium-, or short-term economical impact. These strategies can roughly be divided into three categories: (1) *Market strategies*; such as changed pricing, divestment or branded generics, (2) *Research and Development (R&D) strategies*; e.g. new indications, reformulations and combinations of drugs, and (3) *Legal strategies*; including generic settlements and new patenting (Ding et al., 2014). While market and legal strategies tend to be faster to execute they also have a shorter-term impact of the profitability. On the contrary, R&D strategies are more time consuming to realize but tend to have a longer impact on sales and profitability (Dubey and Dubey, 2009).

This study focuses on the R&D strategy of finding new indications (disease areas) for already existing drugs, also referred to as *repositioning*. The idea of this strategy is to use drug products that are already developed for one disease in additional disease areas as a way of expanding the market. Such strategy will accelerate the R&D process, decrease the risk of failure and give an overall reduction of the product development costs by utilizing developed products with already proven bioavailability, safety and manufacturing profiles (Novac, 2013; Braun et al., 2010).

The repositioning strategy has gained in popularity and has become more important for revenue growth within the industry due to its good prospects of extracting more value from already made investments of developed products (Dubey and Dubey, 2009; Barratt and Frail, 2012; Smith, 2012). The industry has shown a number of successful repositioning projects, where one of the more famous examples is the case of sildenafil, mostly known as Viagra (Kass, 2011). Silendafil was first developed for treating angina, but during the clinical studies the drug showed side-effects of increased erectile function. The discovery was used by the developer who made a decision to expand the market of sildenafil by also selling the product within the indication of erectile dysfunction. This decision show to be very valuable,

as Viagra became a blockbuster drug in this latter indication.

In summary, a company may (through repositioning) use existing resources to increase the economic return on investments made, by expanding into new indications requiring less resources than developing a product from scratch. Such initiatives are becoming more important in an environment where the development output is low and the competitive threat is becoming fierce.

1.2 Problem formulation

The interest of repositioning strategies has increased among both pharmaceutical companies and academia. This has resulted in an increased number of scientific papers discussing the topic of repositioning, although, it is still seen as a relatively unexploited area (Tambuyzer, 2010; Barratt and Frail, 2012). The focus in the existing body of knowledge has been repositioning as a general strategy among other options. With few exception (Barratt and Frail, 2012; Novac, 2013), the knowledge of how such strategy becomes successful and why some products fail before market approval is still scarce.

As the repositioning possibilities often are many and the budget limited, it is essential to make informed and motivated choices. A faulty decision during this process has great negative impact on the return on investment. Hence, it is of interest to master and streamline the repositioning decision-making, ensuring smart choices. To the best of my knowledge such theoretical model is not publicly available.

1.3 Purpose

The purpose of this master thesis is to explore the process of drug repositioning and to develop a repositioning model that could allow pharmaceutical companies to digest available market information and other parameters necessary, to make an informed and smart repositioning decision.

1.4 Research questions

To fulfill the purpose the study intends to answer the following research questions:

1. *What parameters are used as center of analysis for evaluating the potential of new indications in a repositioning strategy?*
2. *How should these parameters be weighted in relation to each other?*

1.5 Contribution

This thesis contributes with a repositioning model based on core parameters taken into consideration during a repositioning process. The development of this repositioning model was enabled by conducting a case study of an ongoing repositioning process at a pharmaceutical company. By contributing with empirics of how informed decisions could be made when faced with the task of choosing between several potent repositioning opportunities this thesis will not only benefit the studied company, but is also useful for any company carrying out a decision of the same characteristics. It is also of interest from a socio-economical perspective, as it enables a sustainable introduction of pharmaceuticals to markets with unmet medical needs.

1.6 Delimitations

This study has been delimited to follow one single repositioning process at a pharmaceutical company. The characteristics of this case is a biologic drug product at the niche market of rare diseases. This differentiates this thesis from other repositioning literature which in general have a focus on traditional pharmaceuticals as chemical compounds for larger patient groups. The study has not taken repositioning projects at other companies, nor other industries, into consideration. Furthermore, the study is also limited to focus on repositioning taken place at a late stage of the life cycle of a currently marketed drug, close to patent expiration. Such repositioning is most common in pharmaceutical industry (Murteira et al., 2014*a*). Repositioning taking place earlier or later during a drug life cycle will thus not be covered in this thesis.

1.7 Disposition of the thesis

This thesis is structured into eight chapters, as follows:

Chapter 1 - This first introduction chapter gives a background to the research problem and stated research questions that are to be answered in this thesis. More specifically it introduces the phenomenon of repositioning in pharmaceutical industry.

Chapter 2 - The second chapter gives a review of current literature on the subject of repositioning and selection methods.

Chapter 3 - This third chapter describes and discusses the methodology used to answer the research questions of this study.

Chapter 4 - The fourth chapter presents the repositioning case that was studied during this thesis with its specific characteristics.

Chapter 5 - In chapter five empirical results from the interviews are presented and answers to the two research questions are given.

Chapter 6 - In the sixth chapter the empirics are analyzed and sorted with current knowledge in literature into a three-step repositioning model

Chapter 7 - This chapter show how the three-step repositioning model can be applied to a real scenario.

Chapter 8 - The eighth chapter aims to discuss the benefits of the presented three-step repositioning model as well as its limitations in relation to current literature.

Chapter 9 - In the ninth and final chapter the conclusions drawn in this thesis are summarized and suggestions to future studies are presented.

Chapter 2

Literature review

This chapter provides necessary background to understand the importance of the contribution of this thesis. It is recommend for readers not familiar with the drug development process to read sub-chapter 2.1, Drug development, as it gives a brief presentation of the process from drug discovery to market, with its bottlenecks and weaknesses. If the aforementioned topic is known to you, you may jump straight ahead to sub-chapter 2.2, Drug repositioning - "exaptation" in pharmaceutical industry, which describes the current knowledge within repositioning strategies. Before the concluding summary of this chapter, the framework of R&D project selection is presented, which has been used in order to create the repositioning model presented in the final parts of this thesis.

2.1 Drug development

The pharmaceutical industry differs from many other industries in regard to its strict regulations, long development times, high costs, and great economical risks. This section gives a brief description of the drug development process with its constraints and risks.

2.1.1 The process from idea to product

To understand the process of drug development a recommended summary is written by Rawlins (2004), in which he discusses the increasing costs in pharmaceutical industry, while following a compound from discovery, through clinical trials, to market. The process is illustrated in Figure 2.1. In brief, the process from molecule discovery to market approval can be explained as follows:

1. *Drug discovery:* Years of research are spent on identifying potential drug-candidates. An approximate number of 5,000-10,000 candidates are found before moving onto the next step of the process.

2. *Preclinical studies:* Approximately 250 promising candidates move onto preclinical studies to be tested for safety in animal models. This includes studies to; (1) determine primary pharmacology (action mechanism and dose-response relationship), (2) discover any secondary pharmacological effects (impact on biological processes other than those intended), (3) explore the pharmacokinetics (PK) of absorption, distribution, metabolism, and excretion (ADME), and (4) study acute toxicity of single and repeated doses as well as genotoxicity (mutagenicity, carcinogenicity).

3. *Clinical studies, Phase I-III:* The drug candidates that passed preclinical studies (approximately five candidates) are now tested on humans during three phases to confirm (1) pharmacological effects, (2) optimal dose range, (3) therapeutic safety and (4) therapeutic efficacy compared to placebo or other available therapies. The first studies are small and the later, larger and more expensive. Clinical studies are also referred to as clinical trials.

4. *Clinical studies, Phase IV:* The drug (usually 1 out of the 10,000 candidates) receives market approval, after which safety information keeps being collected from users. This may reveal side effects that occur after longterm drug use.

5. *Post-market improvements* In this phase the drug is already approved and considered to be safe for its current indication. It is now time for other market strategies to take over, in order to prolong the lifetime of the drug (Ashburn and Thor, 2004).

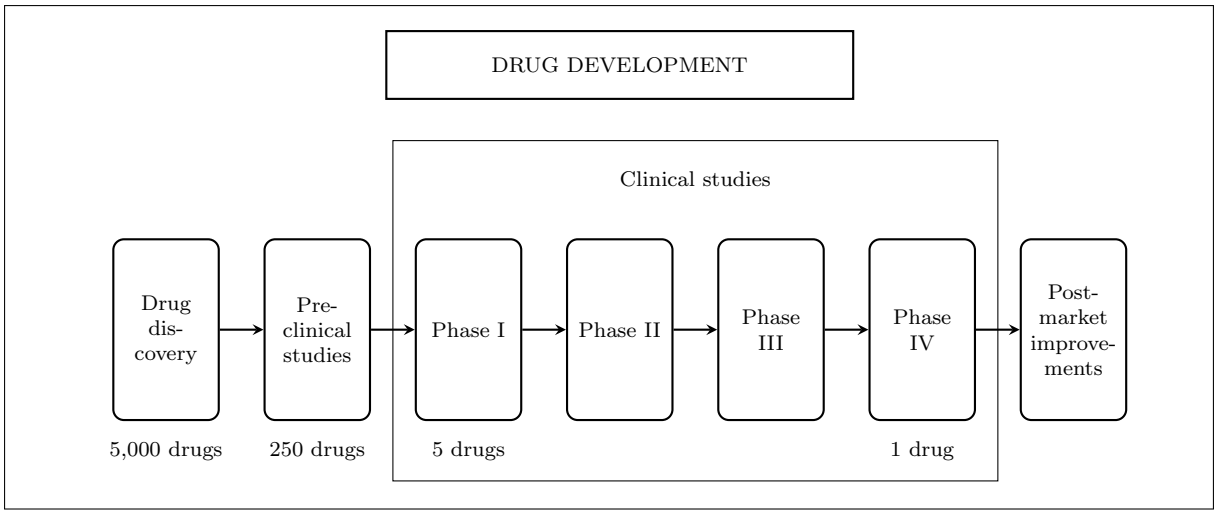


Figure 2.1: The process of drug development.

This process applies to both chemical and biological pharmaceuticals, no matter of market size. What may differ is time and cost of the different phases in the process. However, since it is not of importance to understand the essence of this paper it will not be discussed in more detail.

Each step in the process is evaluated against regulatory requirements before the drug is approved to move onto the next phase. The overall focus during the process is: quality (e.g. excipients, sustainability, packaging), efficacy, and safety. A final approval of the drug will require a shown superiority over existing therapies in respect to quality, efficacy and safety. This is a reason why companies in the pharmaceutical industry strive to be first to the market with a new drug. Being first means a lower approval threshold since superiority only has to be shown over a placebo product (Barratt and Frail, 2012). What is not included for regulatory approval in the United States, but is considered at company level, is cost efficiency. That is, the market prospect of the candidates chance to offer economic value to the company (Rawlins, 2004). Such parameter is however considered for an approval in the European Union, but with focus on how cost-effective the drug is for society (Barratt and Frail, 2012).

2.1.2 Stagnant productivity in pharmaceutical industry

Despite today's great knowledge and technologies, enabling efficient identification of disease targets and drug candidates with great efficacy, the industry still struggles to satisfy the market demand. The main constraint, preventing the companies to produce new drugs to their actual potential, is the large development cost (Barratt and Frail, 2012). The cost of a drug development program has been estimated to be somewhere around 500 million to 2 billion USD (DiMasi et al., 2003; Helmchen and Lo Sasso, 2010; Cowlrick et al., 2011). Moreover, as can be seen in figure 2.1, many drugs will fail and never reach the market. Most of these drugs fail in early development due to safety reasons, but also later in Phase II and III due to low efficacy (in other words, if the drug lacks to show superiority over current treatment or placebo) (Barratt and Frail, 2012).

As an attempt to counteract this trend of low drug output, the industry have sought alternative ways to approval. Some examples are:

1. *Conditional approval:* A drug can be granted a conditional approval before all data has been gathered, if it shows significant benefits compared to existing drugs, for a severe medical condition. This approval is given at a one-year basis and is renewed annually until further clinical studies affirm the efficacy and safety, after which a complete approval can be granted (Carroll et al., 2008).

2. *Exceptional approval:* For rare diseases where it is not possible to conduct an ordinary clinical trial (due to ethical or methodological reasons) some drugs will be approved only based on results from trials on few patient. Such approval has to follow strict rules, such as annual reassessment of safety and efficacy (Carroll et al., 2008).

3. *Generics and Biosimilars:* After a patent expiration other producers can start copying a product. By showing a sufficient similarity of the original drug through pharmaceutical documentation and pharmacokinetics data, a generic product can be approved based on data from the original product. For copies of biological pharmaceuticals, the so called biosimilars, required data documentation is slightly more complex (Gottlieb, 2008; Hou et al., 2011).

These initiatives have also lead to an increased competitive climate with generics and biosimilars entering the market shortly after patent expiration.

This phenomena has miss-shaped the life cycle curve. A regular product would over time go through the phases of development, market introduction, growth, maintenance and finally over to a decline phase where the sales go down (Ellery and Hansen, 2012), this is shown in Figure 2.2. However, the drug life cycle is different. Apart from the development phase which tend to be much longer for pharmaceutical products than for products in other industries, the more important difference for the subject of this thesis is the lack of a maturity phase. Instead of going from growth phase into a stable maturity phase the growth phase quickly transit into a steep decline (Dubey and Dubey, 2009; Ellery and Hansen, 2012). This is shown in Figure 2.3. Due to the shape of this life cycle curve the industry refers to the sudden drop of sales after patent expiry as the "patent cliff".

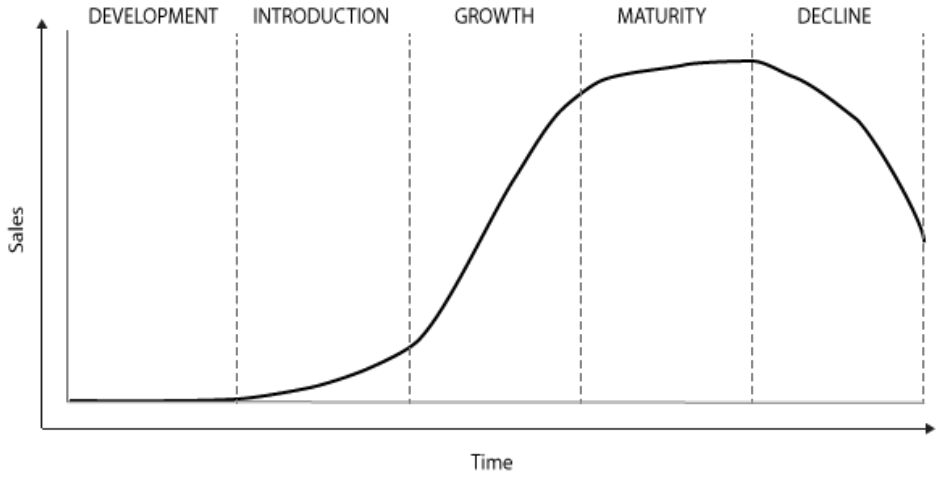


Figure 2.2: Standard product life cycle

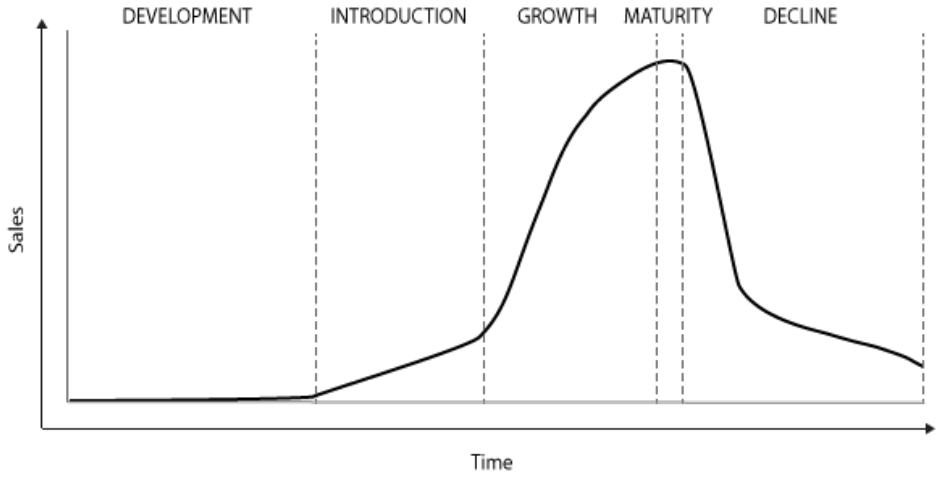


Figure 2.3: Drug product life cycle.

Hence, the high development costs must be covered by the income from sales of the approved drugs during the limited time left of the patent (often only a few years) (Ding et al., 2014; Kvesic, 2008). To recover costs, as well as to gain profit, a marketed drug is estimated to have to bring annual sales of over 500 million USD (Rawlins, 2004). The result of this equation has resulted in drugs that are too expensive to develop and too expensive for consumers to buy.

To re-shape the curve, elongating the maturity phase, pharmaceutical companies have to be innovative. New patents and differentiated products are two ways of protecting the product from a fast decline. This creates entry barriers against generics and biosimilars and prolongs the product lifetime (Dubey and Dubey, 2009).

With the background of the pharmaceutical industry and drug development covered, we can move onto the next subject, the topic of this thesis, repositioning. Repositioning is an innovative initiative used by the pharmaceutical industry to prolong the life of products and increase the return on earlier investments (Novac, 2013).

2.2 Drug repositioning - ”exaptation” in pharmaceutical industry

Exaptations are innovations that initially were developed for a different purpose than what it is used for today. The concept stems from evolutionary biology, where it is used to describe the phenomena of traits shifting function, e.g. our skeleton was first developed to store phosphates, today the main function of the skeleton is to give structural support. This concept can also be used when discussing product innovation, which has been done by Andriani et al. (2016). The authors describe how companies can be innovative by placing their product in a new setting, finding new uses for their existing products. While traditional ”adaptive innovation” refers to the process of creating products as solution to a given problem (satisfying a need), exaptation is the reverse process starting with a solution (the product), then subsequently finding problems the solution can solve (Andriani et al., 2016). The exaptation concept is known under the name ”drug repositioning” (or drug repurposing, redirecting, reprofiling) within the pharmaceutical industry. The idea is to find new indications for an already existing drug and should not be confused with the marketing term of brand repositioning which refers to changing the consumers perception of the product or brand.

Murteira et al. (2013) present a nomenclature for this process, which has been used under many different names and definitions in literature. Their classification complies with the R&D strategies presented by Ding et al. (2014) and the structure is presented in figure 2.4. This thesis uses this nomenclature where *repurposing* is defined as ”[...] all the re-development strategies based on the same chemical structure of the therapeutically active ingredient as in the original product” (Murteira et al., 2013, p. 16), *repositioning* as ”[...] the process of finding a new indication for a drug or compound.” (Murteira et al., 2013, p. 16), and *reformulation* as ”[...] making a particular change in the formulation of the original drug” (Murteira et al., 2013, p. 18).

Another commonly used term is ”line-extension” which in many cases is used with the same definition as Murteira et al. (2013) uses for repositioning. With that said, this thesis will now use the terminology of repurposing, repositioning and reformulation as they are defined above. Figure 2.4 below show the connection between the terms, where repurposing strategies include all re-development initiatives of a product, namely repositioning, reformulation, and drug combinations. This thesis will focus on the phenomena of repositioning.

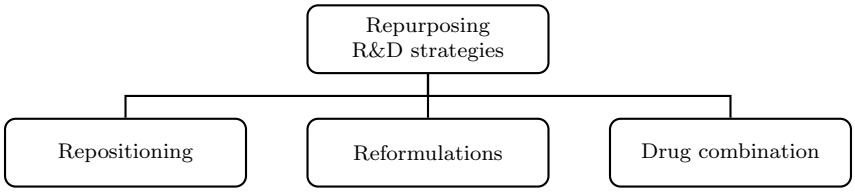


Figure 2.4: Three ways of performing a drug repurposing.

2.2.1 Drivers for repositioning

Pharmaceutical industry is working an uphill battle with high development costs, decrease in R&D productivity, few market approvals and low chances of revenue due to patent expiry and generic or biosimilar intrusion. In an attempt to counteract this, and quickly produce new and commercially attractive drugs at a reasonable cost, the industry has turned to the strategy of repositioning (Ekins and Williams, 2011; Smith, 2012; Ashburn and Thor, 2004).

There are some big advantages with repositioning strategies within pharmaceutical industry. To begin, many diseases share a common pathology (they depend on the same signaling pathway) which gives a drug addressing that pathway a good probability to also be safe and effective in other indications within that specific pathway group. This also means that safety and efficacy documentation from the first indication can be reused in new, repositioning indications. The results from this are shorter development times, reduced costs and decreased risk of failure due to safety compared to a *de novo*[1] development (Barratt and Frail, 2012; Novac, 2013; Ashburn and Thor, 2004).

Repositioning has further the benefit of having the possibility to use the brand and company name. By using the same name as an earlier approved product a quality signal will be sent to clinicians and patients (Ding et al., 2014). Such use will not only decrease the informational costs but also accelerate the speed of market acceptance of the product. Another benefit of conducting a repositioning is that it will attract venture capital partners since more value is created by small means (Ashburn and Thor, 2004). Moreover, legal benefits of repositioning are also making the strategy attractive. A new indication can extend patent life with three years, prolonging the period of profit-making (Ding et al., 2014).

Due to the amount of benefits associated with a repositioning strategy a visible increase in popularity begun around year 2000. Today more than 90 % of marketed drugs are approved for more than one indication (Barratt and Frail, 2012; Ashburn and Thor, 2004). However, there are several paths to take for a repositioning and these are presented in this next section.

2.2.2 The many faces of repositioning

Repositioning has become one of the more commonly used strategies within life cycle management (LCM) and constitutes around 10-15 % of the total R&D spendings in the LCM of pharmaceutical products (Novac, 2013). The strategy may be conducted in many different ways as will be explained below.

Repositioning at different stages of the product life cycle

A repositioning strategy can be applied on drugs already existing at the market or drugs that have been discontinued during the development process, but also for older shelved drugs or as parallel projects for drugs still under clinical development (Novac, 2013). An easy way of categorizing what type of repositioning one talks about is by clarifying if it is a repositioning taking place before or after a market approval. Further, it may also be a repositioning taking place before or after a patent expiry (Murteira et al., 2013). Figure 2.5 show the different alternatives of when to start a repositioning process during the life cycle of the drug.

At what time of the product life cycle the repositioning is performed will slightly effect the procedure and what factors that has to be taken into consideration in order to succeed. For example, if the patent has already expired the threat from generica or biosimilars are greater and the prospect of getting a return on further investments is lower. According to a study made by Murteira et al. (2014*b*), more than 70 % of the repositioning initiatives are done and approved before patent expiry.

Different approaches of finding repositioning candidates

Repositioning has historically occurred through unexpected side effects of the developed drug (Ashburn and Thor, 2004), in a so called serendipitous discovery (Murteira et al., 2013). This was the case for sildenafil (Viagra), that first was developed to be used against angina, but during clinical studies showed side effects of prolonged penile erection (Kass, 2011) and repositioned into that indication.

After the strategy gained in popularity the approach of finding repositioning candidates and indications has become more systematic. Hence, the process is today commonly conducted through high-throughput screening of drugs against diseases in an *in vitro*[2] assay or animal model (O'Connor and

[1] The term *de novo* refers to a process starting from scratch.

[2] An *in vitro* process refers to a biological process performed in a controlled, artificial environment such as in a test tube, compared to an *in vivo* process which is performed in a living organism.

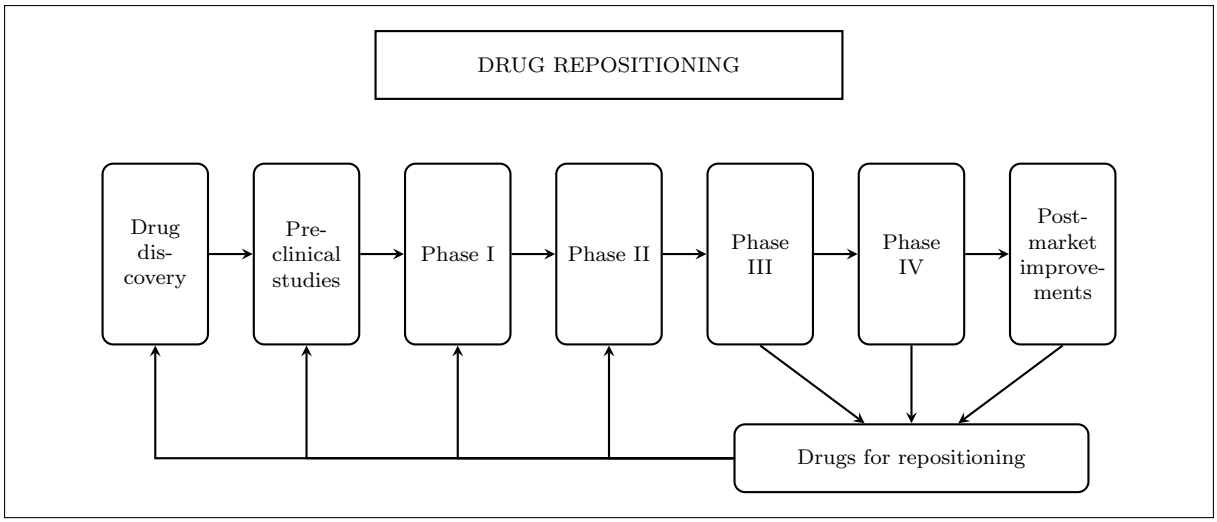


Figure 2.5: Repositioning at different stages of the drug development process.

Roth, 2005). Such screening approach is foremost common among specialist biotechnology companies that possesses technology platforms to perform cost-effective, high-throughput screenings, but is also starting to become part of the strategy of Big Pharma (Barratt and Frail, 2012).

A third approach mentioned in literature is a type of "user innovation" or planned match method. This is an approach where clinicians and academics find pathway relations between indications and from that build a hypothesis of a match between a drug and a new indication. The drug is then used off-label to confirm the hypothesis (DeMonaco et al., 2005). This approach is most common and is, according to Murteira et al. (2014*b*), used in 55-70 % of the repositioning cases.

This gives a classification based on whether the findings are serendipitous, systematically screened, or planned matches. What kind of finding it is, will also have effect on what factors to consider in order to get a successful repositioning. A planned match approach would, for example, not allow for a new patent since the finding is not "non-obvious" (a criteria for a patent to be filed). Any of the other two would be suitable for applying for a new patent since these may give unexpected combinations.

Repositioning targets

The next classification of a repositioning, that may effect the factors to consider in a repositioning model, is what kind of pharmacological target there is. It can either be an "on-target" or "off-target" repositioning (Murteira et al., 2013). An on-target repositioning means targeting the same pathway in another indication while an off-target repositioning targets another pathway in the same indication. The former is much more common (Murteira et al., 2013). Further, many repositioning processes act within the same therapeutic area but a repositioning may also function in a new therapeutic area.

Factors to consider in these different types of repositioning classes are for example competence and external collaborations. By going into a new therapeutic area or even a new indication, new contacts has to be made, both with patients and clinicians.

Reformulation as part of the repositioning strategy

Murteira et al. (2013) divided repurposing into repositioning and reformulation, but as they also stress in the same article, almost 10 percent of the repurposing attempts combine the two groups of reformulation and repositioning into a so called "repositioning aided by reformulation". These cases include a repositioning to a new indication that may require some changes to the product in order to better fit the target patient group in the new indication. Such changes may include a change in administration route, excipients change, a modified release formulation, changed dosage, or a change of structure of the active substance. The latter three may give a new patent to protect the substance while all five would have the purpose of enhancing the patient convenience, or drug efficacy and safety (Dubey and Dubey, 2009).

A repositioning aided by reformulation differs from a regular reformulation since the main purpose of the repurposing is to expand into a new indication. These changes will however require additional

development investments in the product (Dubey and Dubey, 2009), something that is avoidable in a regular repositioning.

Figure 2.6 below shows a classification tree of repositioning. The colored route was the path that was followed in the repositioning case studied during this thesis.

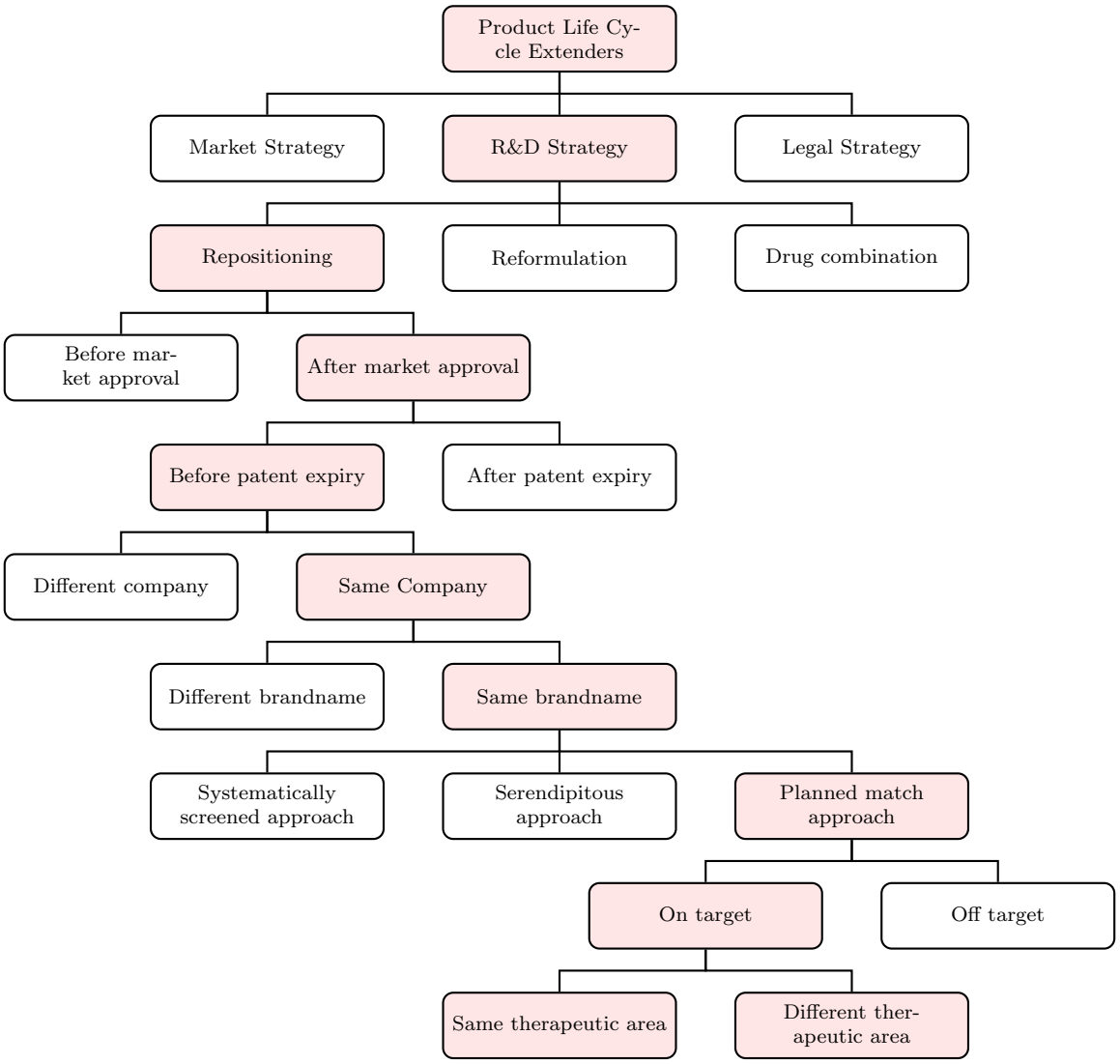


Figure 2.6: Repositioning classification tree.

2.2.3 Challenges with repositioning

Even though the risk of failure is decreased with a repositioning strategy compared to a *de novo* development it is not totally risk free. Each new indication requires extra investments to perform a separate clinical trial, market authorization and reimbursement approval (Tambuyzer, 2010). The general literature of the challenges surrounding a repositioning is scarce, but there are some risk-factors that have been considered in literature. Some factors to take into consideration before starting a repositioning process are;

1. *Safety data:* Since the target patient population might differ from the original product target population, new safety data might be required (Barratt and Frail, 2012). This also applies for situations where new doses are preferred or when the primary indication is an acute treatment and the second is a chronic indication and much longer safety studies are needed. Further, these new studies may reveal unknown properties and safety issues, that can affect the original indication by giving non-relevant label warnings (Barratt and Frail, 2012).

2. *Patent:* Patent possibilities for a new indication are new dosage, new route of administration or a new method of use (Dubey and Dubey, 2009; Ding et al., 2014). Such patent is desirable in order to increase the possibility to receive income during a longer period. However, such patent is not easy to get for an already marketed drug since physicians often conducts single case studies showing effectiveness in a new indication, hindering the company to file a patent for that indication (Barratt and Frail, 2012). To expand the market without having a patent protection may attract generica or biosimilar competition.

3. *In-house competence:* Further, most companies focus on a specific therapy area which means that they may lack competence in the area of the new indication. This will complicate the process since clinical trials require a substantial amount of clinical expertise. The repositioning might therefor require additional collaborations with e.g. contract research organizations (CROs) or clinicians to conduct investigator initiated studies (IIS) (Barratt and Frail, 2012).

4. *Price and payers:* Another barrier for marketed drugs is the different pricing policies for different indications. Pricing and branding in different indication can therefore be challenging (Barratt and Frail, 2012).

5. *Competition:* Threats of off-label competition and generics or biosimilars are always going to be a challenge. In the United States the system allows prescription switching, which means that a drug can be exchanged for a generic copy. The incentive for such change is quite strong since the profit margins go to the wholesalers, retailers and payers in the distribution chain and this margin is much larger for generic drugs than for branded drugs (Barratt and Frail, 2012).

As the investment in a repositioning is not completely risk free and one have to consider development and market risks (Dubey and Dubey, 2009) management might not always be willing to invest more in a product, especially with competing opportunities in pipeline. In order to motivate a repositioning initiative we will now turn to how the literature describes success factors for such a process.

2.2.4 Identified repositioning success factors

Benefits of using a repositioning strategies have been stressed in literature, but how to ensure a successful result is not well researched. Barratt and Frail (2012) is one of few giving a quite thorough description of the phenomena of repositioning, also touching upon some success factors.

First of all, in order to succeed one must make rational decisions. This requires, according to Barratt and Frail (2012), a good understanding of why compounds fail or why they are not approved. By engaging regulatory authorities and payers early in the process the chances of getting an approval increase as changes in regulatory criteria can be detected.

Further, the authors describe how the complexity, cost, and risk of a repositioning program depend on the quality and completeness of existing data in form of toxicology, pharmacokinetics and drug safety profiles. In order to decrease the cost one should look for shorter studies with fewer patients. A high unmet need will also likely lead to faster regulatory and market acceptance than normal. This view is shared with other authors such as Drummond (2008) and Novac (2013) whom emphasizes orphan (rare) diseases being especially beneficial for a repositioning process. Receiving an orphan designation by the regulatory authorities will provide extra incentives such as tax reductions, clinical study design assistance, and market exclusivities.

Some indications will require strategic partnerships to reach necessary competence before expanding into new therapeutic areas, outside the core competence of the company. Such partnership can also help spreading the economic risk of a repositioning program according to Barratt and Frail (2012) and Novac (2013). Collaborations are common with non-profit Patient Advocacy Groups (PAGs) and with Investigator Initiated Research Agreements. The former work with encouraging development of drugs for specific indications (often with a focus on rare diseases) through philanthropic fund-raising. The latter are clinical research programs where clinicians perform and are responsible for clinical studies, while the company solely contributes with the drug (Barratt and Frail, 2012; O'Connor and Roth, 2005).

Murteira et al. (2014*a*) focus on whether repositioning initiatives actually create economic value or not. The concluding results is that any change in administration route, the addressing of an unmet need, and the keeping of the brand name, all have positive impact on price and hence, on creating economic value. These factors may also be considered to be success factors of a repositioning process. Further, Smith (2012) adds to the discussion that success in a repositioning process depends on how both intellectual

property and regulatory exclusivities are gained, since the commercial success depends on these market exclusivities.

Going back to Barratt and Frail (2012), they also stress the importance of having the support from leaders and decision-makers as well as having sufficient resources in order to go through with a repositioning program. I believe that support may be gained by showing a well motivated repositioning choice with good potential. Next section will guide us through some methods used for making such selections.

2.3 Project evaluation and selection

With numerous repositioning possibilities, companies have to prioritize opportunities with the best probable outcome. Such process of narrowing down from several indications to one or just a few, with best potential, is done through a number of decisions.

In general, and also in this repositioning scenario, decisions made in pharmaceutical industry are based on incomplete data, due to economical constrains and practical reasons, making it impossible to map all necessary data (Menon et al., 2015; Cowlrick et al., 2011). These decisions, permeated by great uncertainty, will also be performed under time pressure since time to market becomes crucial close to patent expiration. Even though a faulty decision (during e.g. product development or repositioning) could cause great economical damage to the company, the main impact on these decisions tends to be individual judgment, such as gut feeling, rather than structured approaches and analytical tools (Cowlrick et al., 2011; Jekunen, 2014; Riabacke, 2006). This means that a decision could be made differently depending on who is making it at that specific time. It could therefor be argued that decisions should be made in a more structured way in order to avoid single individual judgment to influence the economic situation of the company. On the other hand one can also argue that such decisions are not taken by a single individual only, but go through several decision steps. Either way, it should be of corporate interest to optimize the decision making and its outcomes. There are a number of analytical tools available such as simulations, algorithms, decision trees or R&D matrices (Jekunen, 2014; Riabacke, 2006). However, the pure access to these tools will not help if they are not adjusted to the decision at hand.

According to Cowlrick et al. (2011) the knowledge of judgment analysis and decision-making related to go/no-go decisions in drug discovery and development is scarce. Looking at the even smaller field of drug repositioning the literature lacks, to my knowledge, a discussion of how a repositioning opportunity should be evaluated and compared to other repositioning opportunities. I will instead turn to the literature of project selection for inspiration. Such decisions have many similarities to a repositioning selection and could therefor be suitable.

2.3.1 Decision trees - a commonly used method within pharmaceutical industry

Cooper (1999) emphasizes in his article the importance of doing the right project as well as doing the project right. This thesis aims to find a solution to choosing the right repositioning project, how to further correctly perform the repositioning, is up to the project leaders.

However, there are eight factors that, according to Cooper, will have great influence on the success of a product project. These start with doing the homework, meaning collecting as much data as possible before the project start. Listening to the customer is another success factor in order to meet their actual need. Third, comes the differentiation necessary to get a superior product, followed by a clear product definition (target market, positioning, features). The focus on the launch cannot be overseen, it has to be well planned and well executed. As a sixth factor comes the funnel process of go/no-go decisions that have to be made in order not to waste resources. Moreover, cross-functional teams with a strong and dedicated leader is also vital for success. Lastly, an international orientation in the new product will enable future expansion of the market.

I would argue that these factors also will be important in a repositioning process. The focus now will however be on the go/no-go decision criteria. This is a commonly occurring decision method in the pharmaceutical industry which is used at certain gates to quickly decide if the project is worth continuing or not (Pritchard et al., 2003; Cowlrick et al., 2011).

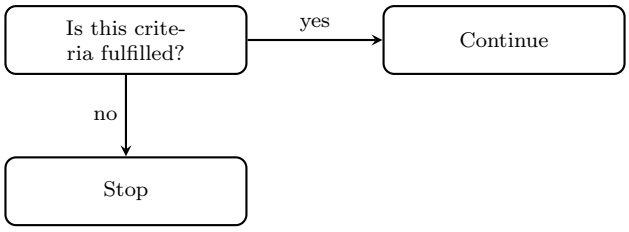


Figure 2.7: Example of a go/no-go decision making.

These go/no-go decisions should, according to Carbonell-Foulqui et al. (2004), be based on one out of five dimensions, namely: strategic fit, technical feasibility, customer acceptance, market opportunity and financial performance. In the case of repositioning the product will be the new indication. Hence, the strategic fit could reflect how well the new indication fits the business strategy, the technical feasibility could be how well the existing product fits the new indication and if any necessary product changes are feasible. Further, the customer acceptance reflects whether there is a patient population in the new indication that is in need of the product. This is closely linked to the question of market opportunity, whether other companies have satisfied the intended new indication. Lastly, the repositioning initiative must result in an income exceeding the necessary investments, the financial performance. The greatest risk with these decisions is that many companies fail in killing projects lacking potential, mostly due to unclarities in the definition of the decision criteria (Cooper, 1999).

Cooper (1999) also presents a number of selection criteria, very similar to the ones presented by Carbonell-Foulqui et al. (2004). Cooper's criteria are: (1) reward, in other words, the profitability, payback period and time to commercialization, (2) business strategy fit, (3) strategic leverage, e.g. product lifetime, position, synergy with other products, (4) probability of commercial success, including criteria such as marked need, market growth rate, competition, regulatory/social/political impact, and (5) probability of technical success, more exactly, if there is a technical gap, the level of complexity, in-house skill and knowledge.

Similar criteria tend to re-appear in different methods of selection models. Table 2.1 shows an excerpt of these. What researchers agree on is the importance of finding the adjusted decision criteria for the project at hand, and also to decide each factors relative weighting. Carbonell-Foulqui et al. (2004) made an attempt to weight the relative importance of the five dimensions in the go/no-go decision process of developing new, highly innovative, products. The study shows that early decisions (at the idea stage of the product development process) often lack the financial criteria while the strategic fit has great importance for approving the new product concept together with the technical feasibility.

2.3.2 Scoring models - a user-friendly R&D project selection model

R&D project selection could preferably be used as an analytical tool to prioritize among different repositioning opportunities. Such tool is used for making decisions under great uncertainty where the setting of the project will change several times before the final stage is reached (Costello, 1983). This has great similarity to the situation of a repositioning initiative. Another similarity is the purpose of allocating limited resources to best potential projects. A big difference though, is that R&D project selection takes place early on in the life cycle of the product, while the repositioning selection studied in this thesis takes place at a very late stage of the product life cycle in an attempt to prolong it. However, this field may be used as inspiration in the shaping of a repositioning selection model.

The field of R&D project selection is extensive and one could summarize its story by saying that the first selection methods were based on quantitative, economic tools (Liberatore, 1987) while later methods also value qualitative parameters to capture the complexity of the environment (Lopes and Flavell, 1998; Meade and Presley, 2002; Tan et al., 2011).

Many authors keep this division, separating methods on their degree of quantitative (economic) and qualitative (strategic) aspects. One of these is Archer and Ghasemzadeh (1999). Another one is Verbano and Nosella (2010), who reviewed the main selection methods used. According to the authors, the methods span from being strict quantitative, using quantitative data as input which through algorithms will result in quantitative outputs, to the other extreme of being purely qualitative methods, comparing opinions of several actors. Baker and Pound (1964) is another well cited article which divides the R&D selection models into three types, *decision theory*, *economic analysis*, and *operational research*. The latter

Table 2.1: Categories used in project selection models

Researchers / Category	Cooper 1999	Carbonell-Foulqui et al. 2004	Liberatore 1986	Verbano & Nosella 2010	Costello 1983	Mottley & Newton 1959	Henriksen & Traynor 1999	Lopes & Flavell 1998
Strategy	Business strategy fit, Strategic leverage	Strategic fit	Corporate objective	Strategic factors, Project portfolio	-	-	Relavence to organization's mission	Strategic analysis
Technology	Probablility of technical success	Technical feasibility	Research and Technology	Technological factors	Technical uncertainty	Technical success	Research return, Technical reasonableness	Technical analysis
Economy	Economic reward	Financial performance	Financial	Economic return	Economic uncertainty	Estimated cost of the project	Business return	-
Market	Probablility of commercial success	Market opportunity	Marketing and distribution	Market factors	Commercial uncertainty	Expected market gain, Strategic marketing need for the research	-	-
Other	-	Customer acceptance	Manufacturing, Timing	Risk and uncertainty level	-	Time to project completion	Risk	Political, social, environmental and managerial analysis

two have a heavy focus on forecasting a detailed profitability of the project options, in the latter, using mathematical programming. Decision theory on the other hand considers several factors in addition to the economic value, using a scoring model.

The methods reviewed by Verbano and Nosella (2010) were evaluated through eight factors: *economic return*, *technological factors*, *market factors*, *strategic factors*, *risk and uncertainty level*, *project portfolio*, *technological factors*, *difficulty of using the model*, and lastly, the *cost (time) of using the model*. Depending on the purpose of the selection one model would be more suitable than another.

In conclusion, a scoring method would be most suitable to our task of performing a repositioning selection. First of all, such a method is suitable for a situation where the R&D project is incremental, the market is either unknown or known, and the technology is known (Verbano and Nosella, 2010). The scoring model will further consider both technical and strategic factors, risk level and market potential, while it also is easy and cheap to use. The drawback of a scoring method is, according to Verbano and Nosella (2010), its lack of focus on economic return. To also get that feature a decision analysis model may be more suitable, such as an analytical hierarchy process (AHP). However, these models are more time consuming and, more importantly, more suitable for radical R&D projects with a new technology (Verbano and Nosella, 2010), not features of a repositioning project.

A scoring model will further require a subjective weighting of a set of parameters decided for the specific process. This subjectivity is considered to be a weakness by some authors (Liberatore, 1986). However, as both (Mottley and Newton, 1959) and (Dean and Nishry, 1965) claim, a judgment from knowledgeable people is sufficient in order to rate projects. The weighing will be according to each parameters relative importance to the decision. Each option is by the weighing given a total score which can be compared to other alternatives. What differs between Mottley's and Newton's focus on research leading to the development of new products and a repositioning process is that the latter is a much more incremental development. This means that the data on cost and expected outcomes are more reliable and the parameters used in such processes may be more detailed.

Table 2.2: Example of scoring matrix

Selection criteria	Option A	Option B	Option C
Blue	5	1	1
Big	2	2	5
Heavy	1	3	5
Total Score	8	6	11
Rank	2	3	1

In general, methods that are too complicated to use, hard to understand and require large amount of data, tend to be ignored by management. The same goes for complex mathematical, computerized systems (Costello, 1983; Verbano and Nosella, 2010). Hence, a more hands-on method will be in focus for the repositioning model in this thesis. Necessary criteria will first be identified and then weighted in relation to importance as well as the quality of the available information, giving a ranking of the repositioning opportunities at hand.

2.4 Chapter summary

After an introduction to drug development in pharmaceutical industry, this chapter gave a review of existing literature of the field of repositioning in pharmaceutical industry, as well as selection models used for product selection in R&D projects.

In summary, many companies turn to repositioning strategies in order to mitigate the effect of patent expiry and low production out-puts (Novac, 2013; Dubey and Dubey, 2009; Barratt and Frail, 2012). While the repositioning strategy has gained interest among stakeholders in the pharmaceutical industry the public literature is still scarce. Murteira et al. (2013) tried to harmonize the use of the terminology while e.g. Barratt and Frail (2012); Novac (2013) gave examples to historically successful repositioning initiatives. What is lacking in the current literature is a hands-on model for choosing an indication with the best medical and commercial potential for repositioning.

With the selection of tools presented in this chapter, in combination with repositioning knowledge, a framework can be shaped to create a valuable repositioning selection model. This framework will be supported by a list of important repositioning factors identified in this case study.

Next chapter will describe how this study was conducted in order to fulfill the purpose of this thesis, creating a repositioning selection model.

Chapter 3

Method

This chapter gives an overview of the research process of this master thesis. Starting with a presentation and justification of the research design followed by how data collection and analysis was performed. The chapter ends with a discussion of the overall strengths and weaknesses of the study as well as the ethical aspect of it.

3.1 Research Design

This thesis aim to explore the process of product repositioning in pharmaceutical industry and to create a repositioning model to support smart market choices. To answer the research questions - *What parameters are used as center of analysis for evaluating the potential of new indications in a repositioning strategy?* and *How should these parameters be weighted in relation to each other?* - a qualitative case study of an ongoing repositioning process was conducted. By relating existing theory and empiric experience I hope to contribute with a deeper understanding of the complex phenomena of decision-making during a repositioning process.

The choice of a single-case study enabled a deeper understanding of the many aspects of the case, capturing the complexity of the repositioning phenomena (Blomkvist and Hallin, 2014). The case has been used to detect the parameters and their internal weighing for a repositioning selection. Further, the qualitative case study was partly joint with an action based research in order to evaluate and improve the repositioning model that was developed based on the collected empirical data.

3.2 Data Collection

There are different approaches for data collection when conducting a case study. This thesis is based on a literature and theoretical review, a market and technical analysis as well as interviews. By using different approaches for collecting empirics I increased my own understanding of the phenomena, which enabled me to provide answers to the stated research questions (Blomkvist and Hallin, 2014). The different methods used to collect necessary empirical data in order to create the repositioning model were used in an iterative manner. They will now be presented in more detail.

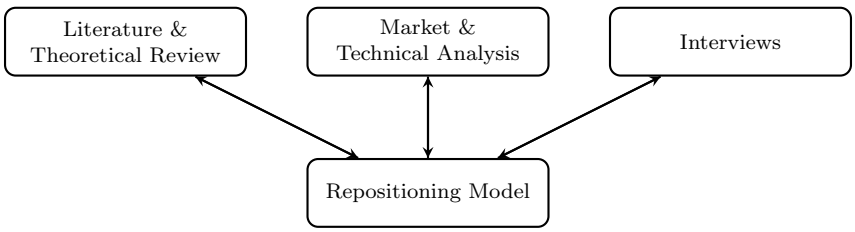


Figure 3.1: Research method.

3.2.1 Literature and theoretical review

To give a background to the phenomena of repositioning as well as an understanding of the factors which decisions are based on, secondary data such as books, articles, government websites etc. have been used. By reviewing the existing literature of the topic of repositioning it became clear that a repositioning selection model, based on a real life case, could benefit the public body of knowledge. Hence, further review of decision-making literature, later focusing on scoring models and go/no-go flowcharts, was made.

Searches of literature were made through scholar databases (KTH Primo, Google Scholar, JSTOR) with search words such as "repositioning", "repurposing", "new indications" "life cycle management", "decision-making" in combination with "drugs", "pharmaceutical industry". By studying reference lists in relevant articles the search was guided forward. Larger emphasis was made on literature written by frequently cited authors and recent publications. All collected articles were critically evaluated, meaning: read and reflected upon in terms of use of key terms, purpose, methods used, supported argumentation and conclusions (Collis and Hussey, 2014). The material was further affirmed by other sources.

As the literature review continued, following the study from day one to completion the search became more and more specific. It started as a help to define the research questions and has later been used for shaping the theoretical framework and to understand the empirical data.

3.2.2 Market and technical analysis

The performed case study included a conduction of a market and technical analysis of a subset of the potential new markets identified for the ongoing repositioning initiative. This was an important element in order for me to increase my understanding of what kind of information that is *de facto* available and their relative importance. This knowledge was later used in the creation of the repositioning model.

The subset of potential markets consisted of three new indications (later referred to as Indication A, Indication B, and Indication C) that had been identified by the case-company. These three had, after a quick overview by the company, shown great potential and were therefor chosen.

Empirics were then collected from secondary and primary sources such as scientific papers, completed and ongoing clinical case studies, patient group forums and through communication with employees at the case-company whom had been in contact with treating clinicians. These sources are scarce since the connections between the drug subjected for reposition and the intended indications are fairly new. Hence, the selection method was simply to read what was publicly available in full text format of "the drug/competitor drug + indication" at scholar databases (KTH Primo, Google Scholar) and websites (clinicaltrials.com, who.int). Further, more data was collected through the access to unpublished IIS (Investigator Initiated Studies) through the case-company, and from participation in internal meetings addressing the topic.

Data was added to the market and technical analysis throughout the study, starting with a search of the technical field in order to understand the mechanism of action of both drug and indication, to further understand the data produced through clinical studies (IIS) and the actual patient need through patient-group forums. This resulted in a business case for for each indication.

In the end, this data collection method had the purpose of giving inspiration to the creation of the repositioning model as well as for showing an example of how the repositioning-model may be used. Gaps in this analysis were filled through interviews with employees at the case-company, discussing the prospect of respective indication. This is further described in the following section.

3.2.3 Interviews

To confirm and improve my contextual understanding of the repositioning phenomena, interviews were performed. Interviews are effective to use for understanding individual views (thoughts, feelings, actions) of a phenomena (Blomkvist and Hallin, 2014; Collis and Hussey, 2014). Since I am interested in the process of evaluation and choice it is preferable to understand the thought-process of the persons involved in the repositioning, and interviews were therefor suitable. This is also confirmed by Riabacke (2006) in their research. Since the repositioning includes several people with complementing competencies at different positions within the company I aimed to cover the whole phenomena from research and pipeline strategy to market potential. I had two to four interview subject from each discipline (R&D, regulatory, clinical studies, commercial, and pricing). The choice of talking with several persons in similar positions was made to reduce bias. Further, these interviews, apart from one exception, were conducted one-to-one to avoid the participants to influence each other, which otherwise is a risk when using for example focus

groups (Blomkvist and Hallin, 2014). The mentioned exception was also the only interview performed over Skype, this due to geographic constraints since the subjects work at the Swiss respectively UK office.

The interview subjects where chosen after their position and competence through a "snowball" selection (Collis and Hussey, 2014), where one interviewee guided me to the next contact. To further confirm their appropriateness as interviewees for this study all participants were asked about their experience of the phenomena of repositioning at their position as well as how well they know the drug product and selected indications. All subjects had experience of former and/or present repositioning initiatives, they knew the product well and were also familial with the indications. Table 3.1 presents a list of the interview subjects. More details of the interviewees are presented in Appendix A.

Table 3.1: Conducted interviews divided into competence area.

R&D	Clinical Studies	Regulatory	Commercial	Pricing
Principal Scientist	Clinical Program Manager	Regulatory Affairs Manager I	Product Group Manager	Global Director Health Outcomes
Senior Director Biomedical Science	Clinical Program Leader	Global Regulatory Affairs Manager	VP Global Brands	Nordic Patient Access Lead
		Regulatory Affairs Manager II		External Affairs & Patient Access
				Global HEOR & Country Patient Access Lead

These semi structured qualitative interviews where all focused on the theme of repositioning, they were however adjusted to fit the area of competence of each interviewee (regulation, strategy, market, R&D, pricing, etc.). In Appendix B you may find the interview template. Since the term "repositioning" can mean different things to different people the definition used in this paper, by Murteira et al. (2013), was described to the interviewees to initiate the open questions. Thereafter, the interviewees started by talking freely around the subject of repositioning and what parameters the interviewees found essential in order to make a choice between different opportunities. Then we focused the interview to the three indications at hand using the perspective of the professional role of the interviewee. Information from this section was used to fill gaps in the market and technical analysis as well as for the creation of the repositioning model. The interview was then wrapped up by asking the interviewee to grade the importance of some identified factors on a "grading list", in order to evaluate the potential of the opportunities in a so called structured survey (Blomkvist and Hallin, 2014). This last step gave quantitative data that could be used in the creation of the repositioning model. By giving this task in the end of the interview it helped to specify and understand the received empiric material.

All interviews were recorded (by permission from the interviewee) and was transcribed shortly after the interview in order to recall and note all impressions from the interview. After this, the template was adjusted to enhance the quality of it and new identified factors were added to the grading-list. In cases where clarification was needed the interview was followed up by email where specific details could be confirmed and misunderstandings reduced.

3.3 Data Analysis

Data has been collected from primary and secondary sources with focus on identifying key factors to take into consideration when prioritizing among potential repositioning opportunities. The process has been iterative with the goal of creating a repositioning model. In short, key themes have been identified in literature and interviews separately. After a comparison of the two, these themes have been categorized under key dimensions to structure the great amount of information. Further, the weighting of identified parameters is primarily based on empirics from the conducted interviews.

Such approach is called content analysis, meaning that similarities and differences between interviews have resulted in a number of identified themes. This was further compared to previous research within the field of drug repositioning. The study tried to keep a conventional content analysis approach where themes were identified solely from open-question interviews (Hsieh and Shannon, 2005). Coding was further done by reading the transcript, high-lightening keywords that in the next step were categorized under themes. These themes were not predefined as in a directed content analysis but may have been unconsciously inspired by literature.

By combining results from interviews with earlier research on the subject, the first research question could be answered - what parameters that are used in a repositioning evaluation. To further answer the second research question - how these parameters should be weighted - the grading from the interviews were analyzed with comments on interdependencies. The results from the market and technical analysis had the function of testing the model against a real case.

3.4 Research quality

Strength and weaknesses of the research may be evaluated by looking at the validity and reliability of the research design, data collection and data analysis (Collis and Hussey, 2014). The question to ask is simply if the research *studies the right thing in the right way* in order to give answers to the research questions (Blomkvist and Hallin, 2014).

3.4.1 Reflections on research design

When forming the research design I had to take into consideration the constraints of limited time, access and resources. Due to the characteristics of the research question, comprising a complex and quite large phenomena, I chose not to conduct an observational data gathering method. To follow the entire process from start to finish would have required a much longer timespan than the time given to write a master thesis. An alternative would have been to study several repositioning projects at different points of the process, this is however an extensive process given that most pharmaceutical companies keep their confidentiality high. If not being restricted by the time frame or confidentiality constraints by the industry it could have been interesting to observe the process from start to goal in combination with an action research design to find potential areas to improve and to further develop a sustainable repositioning-model.

However, by choosing a case study I was given the possibility to explore the phenomena in its natural setting (Collis and Hussey, 2014). This single-case study of an ongoing repositioning process gave sufficient data depth in order to create a detailed repositioning model used as an early guidance in choosing between opportunities. Giving a detailed picture while having a broader focus on several products and/or companies would have been harder.

Although a single-case study will limit the generalizability of the concluded results (Blomkvist and Hallin, 2014) the generalizability is slightly increased by the Chapter 4, which presents the context of the case.

3.4.2 Reflections on data collection

Bias was reduced and the validity improved by using a triangulation method for data collection (Collis and Hussey, 2014). The large spectra of information (market and technical analysis, in combination with data from literature and empirics from interviews of key persons in the repositioning process), gave a deeper insight of the phenomena under study.

Secondary sources were picked from established journals through a well planned literature search by year, citations and name to increase validity. Primer focus has been on documents treating strategies behind repositioning as well as clinical studies used in the technical and market analysis. The use of documents is valuable in highly regulated industries such as the pharmaceutical sector.

Further, when choosing respondents for the interviews the validity of the results were considered and respondents were selected based on their competence (through work titles and recommendations from other interviewees) (Collis and Hussey, 2014), this competence was also confirmed by affirmative questions initiating the interviews.

The interview was further continued with open questions, which reduced bias from the interviewer (Hsieh and Shannon, 2005). To further increase validity, probing questions were used to assure understanding. All interviews ended with asking the interviewees to grade a list of factors. This grading did

not give a statistically proven result due to the small size of the responder group, it did however give a good view of this certain case under study. To solely use surveys was not an alternative since my objective was to give an in depth understanding of the decision making taking place during repositioning rather than giving a general view of the parameters of interest during decisions-making. By providing the grading-lost after the open questions the bias from the interviewer was further decreased.

In order to increase the reliability the research process has been described and the interview template has been attached in Appendix B.

3.4.3 Reflections on data analysis

Even though this research was conducted by a single researcher the subjectivity has been kept to a minimum. All interviews were recorded and transcribed, minimizing the risk of own interpretations on questions discussed. Each interview was also followed up by email where specific details could be confirmed and misunderstandings reduced before the data was transferred to respective theme. In this way reliability was improved, since the unambiguity in the interpretation of the empirical data was decreased (Blomkvist and Hallin, 2014; Collis and Hussey, 2014). Further, the results were validated through continuous discussions with supervisors at the company and from KTH.

When using a conventional content analysis method there is a risk of not understanding the context and hence key categories can be lost in the process, thus affecting the reliability of the results (Hsieh and Shannon, 2005). There has also been a risk with having interviews and literature research running in parallel, and the interview questions and hence themes may have been unconsciously biased by literature. Being aware of this risk has however decreased its impact on the results.

The range of respondents might have been too narrow to give a substantial amount of data in order to draw valid conclusions. From this sample group data saturation was however obtained, with the reflection of the limited geographic dispersion of the interviewees. The data triangulation that was used, interviewing several employees within respectively field, increases the reliability (Collis and Hussey, 2014).

3.5 Ethical considerations

Important to note is that this research has been conducted and thesis has been written at the case-company. This means that I have attended meetings and conversations treating the subject of repositioning Zepophan into Indication A/B/C. However, due to ethical reasons, the empirics building this thesis is only based on what has been found in documentation and said during the official interviews. What has been learned by the side has in cases been addressed during interviews as well, meaning that the result of this thesis is presented in a truthful way, not hiding anything of importance.

This takes us further to the subject of confidentiality. This thesis has been written under a confidentiality agreement why the company, drug and indications have been given alias names. However, I want to state that this has not conflicted with the essence of this thesis since specifics of indication and pharmaceutical is not of interest to understand the phenomena of repositioning in pharmaceutical companies. One could argue that this would decrease to possibility to generalize these results to other settings. I have, however, presented all necessary details of the company and process to give the reader a chance to decide if the results could be used in another situation as well.

All interviewees are also presented with title only so that data can not be tracked to a named individual. Further, all respondents were also informed of how the recorded and written material were going to be managed during and after the study.

3.6 Summary of method

To be able to answer the research questions of this thesis, a single-case study was performed of an ongoing repositioning project at a middle sized pharmaceutical company. Data was collected from current literature on the subject of drug repositioning as well as from interviews and a technical and market analysis of the drug and three possible indications. In order to understand the complexity of the phenomenon of repositioning areas of research and development, clinical trials, regulatory, commercial, and pricing has been studied. By working with data triangulation the validity of the findings has been strengthen. The author has also consciously been working with reliability in all steps of the process in order to increase it. In the following chapter the context of the case-study will be presented. This may enable the reader to generalize the results of this study and apply it to other, similar, cases.

Chapter 4

Empirical setting of the repositioning process under study

This chapter gives a short description of the repositioning case that was studied in order to answer the research questions of this master thesis. By presenting the characteristics of this case the chapter may help the reader to determine the generalizability of the results of this thesis.

4.1 Zepophan - a case of repositioning

In order to understand the repositioning process a case study was conducted on an ongoing repositioning process at a pharmaceutical company, in this thesis called *Zepo*. Zepo is a middle-sized international pharmaceutical company specializing in innovative treatments and services for patients suffering from orphan (rare) diseases. Due to the small target group of orphan drugs the chances of return on large investments are fairly small, which historically has made this niched market unattractive (Tambuyzer, 2010). Further, Zepo invests in all phases from costly research, clinical trials and production, to marketing and sales and the need of increasing return on already made investments is urgent. In effort to increase the revenue Zepo is now actively working on the strategy of finding new disease areas of which their already developed products shows efficacy. In their current repositioning process they aim to reuse an already approved and marketed drug (in this thesis referred to as *Zepophan*) for new indications, the repositioning path is illustrated in Figure 4.1. The company has received numeral suggestions of possible new indications for their product from clinicians through IISs and off label uses in single clinical case studies performed by treating clinicians.

This case can be seen as an ideal repositioning candidate since it comprises the following characteristics;

1. The repositioning in this case study refers to a reuse of an *approved and marketed drug* in a new indication. This means that safety and toxicity data is available, which may be used in order to decrease the development time and cost.

2. Zepophan is a *biological molecule*, indicating that the threat of cheaper copies is smaller than for "standard" (chemically produced) drugs. This is due to the more complex production and documentation necessary to produce a biosimilar compared to a generic drug production, making this process harder and more expensive to copy (Dubey and Dubey, 2009). A drawback of being a biologic product is that any change in the process or dosage form may cause changes to the molecule, and additional safety and efficacy studies may be necessary (Dubey and Dubey, 2009).

3. Due to the *company size*, the revenue requirement is lower than for Big Pharma. This is advantageous since it gives several repositioning opportunities within areas with smaller revenue potential where Big Pharma is not interested to compete.

4. The company is focusing on *rare diseases* which is a valuable factor for both receiving an approval and for reducing the development time. This is due to the generally high unmet medical need surrounding rare diseases which means that available therapeutics are few and thus the approval threshold lower and regulatory times shorter compared to disease areas with acceptable therapeutics

available. Moreover, there are even more incentives available if receiving an orphan designation, such as tax and fee reductions (Dubey and Dubey, 2009; Tambuyzer, 2010).

As the case show to be suitable for a repositioning process one can assume that repositioning is commonly used in such settings, which also makes this specific process interesting to study for the purpose of this thesis, to create a repositioning model.

Factors that complicates the case, but which are not necessary unique for this specific repositioning, is Zepo's open view to different outcomes in regard to e.g. pricing, brand name, and collaborations. This openness complicates the choice and it becomes even more essential to be able to weight different parameters in order to rank the opportunities. The goal of the repositioning process is to balance risks and maximize return. While most companies would set the profit as priority Zepo asks to take into account the medical need and situation of the patient, which is more important than maximal value. Such thinking is in line with the business plan and company mission of maximizing value for patients.

Three new indications were studies for this repositioning case with Zepophan, called "Indication A/B/C" and more details about the these are presented in Appendix C.

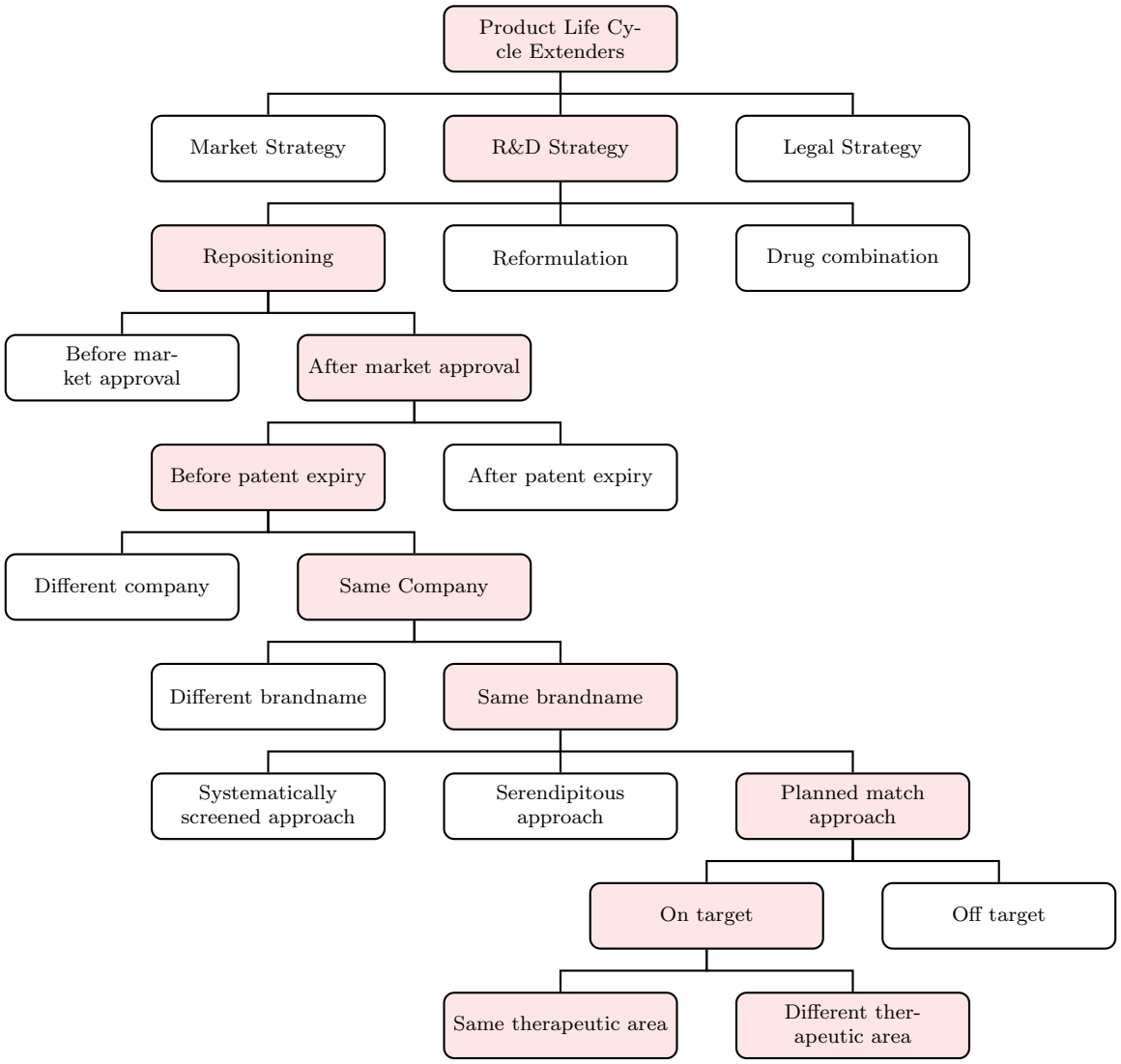


Figure 4.1: Repositioning path followed during the case study of Zepophan.

Chapter 5

Empirical findings

In this chapter you will find the empirical results from the case study of the repositioning process of Zepophan at Zepo. All findings derive from conducted interviews and documents used for the analysis of market and technique. Citations from interviews not held in English have been translated by the author.

5.1 Key parameters in a repositioning strategy

In order to focus scarce resources toward the disease candidate with a promising future there are many factors to consider. From interviews with experienced employees involved in the repositioning process key parameters to contemplate in the evaluation of a repositioning opportunity were identified.

From the conducted interviews one can find six main categories; (1) Medical need, (2) Economic return, (3) Scientific support, (4) Timing, (5) Life Cycle Extenders and (6) External relations. These categories will now be described in more detail with associated subcategories.

5.1.1 Medical Need

When asked the question, "what parameter the respondent would consider first in a repositioning process", the majority gave the same answer: *the medical need*. This concept was described by the Global Regulatory Affairs Manager as a life threatening or chronically debilitating disease that today lack treatment, or have a treatment which is not showing optimal efficacy or causes severe side effects. The Clinical Program Leader also added convenience and access to the list. Convenience implies how pleasant it is for the patient to take the drug, e.g. if the patient has to be hospitalized for weeks in order to be treated it is much more inconvenient than if the treatment can be taken at home. Further, the availability of the product may be limited due to a out of range price of the product or if the product lack approval for the indication.

Hence, if large, the medical need play an important role for many functions. For example, the regulatory authorities approval time may be shorter for an indication with a high unmet medical need. Less data will be needed before approval, meaning that the regulatory authorities will allow shorter and smaller clinical programs where additional data will be presented after the drug is marketed. From the commercial perspective the unmet medical need equals a market opening. Further, the Principle Scientist argued that even if the business case would not be positive it would be valuable from a socioeconomic perspective to reposition into an indication with an urgent medical need.

"On one side of the scale we have the size of the patient population and on the other side we have the patient need. The larger population, the more interesting is the case. And a large medical need, with no other available treatments, indicates a market opening for us." - Product Group Manager

"In the end it is all about the medical need. Where is the value greatest, with best effect compared to the cost. This makes it easier to reach the market and to get the price approved." - Nordic Patient Access Lead

Subpopulation

Focus on finding a medical need is also apparent in the research & development stage. The search for "transformational molecules" is in focus, meaning a search for molecules that show superior efficacy over

other conventional treatments. Such effect is according to the Principal Scientist shown in specific, well defined, patient groups. Filtering out that subpopulation, showing good efficacy with the drug in the intended indication, can be the difference of considering the drug to be life-saving or not. This will, as shown later, have affect on both pricing and approval.

Further, in order to find the right subpopulation for the treatment there has to be a validated biomarker that can identify individuals belonging to that population. If there is no biomarker the risk of not reaching the patients in time increases.

"Finding a way to diagnose is important in order to be a first line treatment for the right subpopulation." - Product Group Manager

In summary, a great medical need will according to the interviewees decrease the clinical study and approval time while it indicates a commercial opportunity. How much it will affect the business case will depend on how great this medical need is. Aiming for an indication with a great medical need will also increase the support from society as a whole.

5.1.2 Economic return

All interviewees mentioned the potential of economic return on a new indication, the "business case".

"We do not want to invest time and resources in something that in the end will not fly." - Principal Scientist

"Sure it may cost that and that much but in the end it is the revenue that matters." - Clinical Program Manager

"The business case must be solid."- Global Director Health Outcomes

"It all comes back to the business case." - Nordic Patient Access Lead

This potential of economic return is simply the calculation of revenue minus costs. Therefor the VP Global Brands suggested that the repositioning effort should be directed towards a large market with high unmet medical need with non-complex development demands from patients and regulatory authorities. Such market is often found in the United States, which has shown to be a better market to get return on developing programs, foremost due to their situation of free pricing and their large population (making it easier to find patients). The free pricing has resulted in a three times greater price of Zepophan in the United States than in Europe.

"If we have a good case in the United States we can push the green button and go for it." - Product Group Manager

Further, it was argued that the potential price of development and necessary regulatory efforts can be estimated from earlier experience while the potential revenue is harder to foretell. It is especially hard to estimate the number of new possible patients in each market since also off-label sales are subsidized in some countries (e.g. in the Nordic countries). This means that the target patient group may already be included in the customer group and receiving an indication at that market would therefor not effect the sales greatly. In Great Brittan on the other hand, and in other big countries in Europe, the patient number is quite straight forward since only drugs having the indication can be sold at a subsidiary price.

The business case should preferably be positive in order for the company to go for a certain indication. There is, however, an option of considering "goodwill" where studies are conducted with the pure purpose of building a reputation of Zepo as a credible, long-term partner. This option is however constrained since Zepo is a listed company with the pressure of delivering positive results every quarter.

Development

As part of building the business case, product development has to be considered. Changes of the product will affect the time and cost to market in a repositioning initiative. However, some changes might be needed in order to increase the attractiveness of the product in the new indication (for payers and patients) as well as for extending patents or to be given market exclusivities. What can be discussed in

terms of development of the product is the change of half-life, different administration route, change in formulation, or a different dosage.

The short half-life of Zepophan has its benefits, giving the drug a better safety profile than its immediate competitors. This has in earlier cases affected the approval. There are, however, indications where a longer half-life would be preferable (chronic diseases where a daily subcutaneous injection is not optimal). For such cases it could be of interest to prolong the half-life of Zepophan. Such attempts has been made but the changes interrupted the interaction with the target, decreasing the efficacy of the drug. In theory it is however still possible and therefor an option to consider.

"If the medical need is urgent and people are dying at a young age one can imagine to go the extra mile to bring about something." - Principal Scientist

Increasing the dosage can also be required when expanding to a new indication. If it is possible or not depends on the molecule size, the maximum volume of injection, and the stability of the molecule in such concentration. In the case of Zepophan the concentration is not considered to be a limiting factor. A change in dose (a more concentrated formula) would give an opportunity to launch the product at another price as a new brand.

"Changes in Target Product Profile are a matter of business case, to concider what changes that are actually worth making." - Regulatory Affairs Manager I

Any changes in the product would however result in longer approval times, up to 12 month, as well as longer clinical studies, and pricing and reimbursement negotiations. A regular repositioning, without any reformulation, would get approval within 6 month and in some countries the price would not have to be renegotiated, according to the External Affairs and Patient Access Manager. A regular repositioning is therefor a safer alternative since the risks of failure is much lower. Also, a change of the product will require large investments on a product with already low margins. The Product Group Manager saw an other side of the case, that is that any investment made in the product is good since it sends a signal to customers and shareholders that they believe in the future of the product.

Clinical studies

The business case is further based on early and superficial estimates of time, cost, and necessary resources of the clinical program. This estimation is in turn based on experience from similar indications. A more thorough analysis of the clinical program is resource-intensive and is not done until the medical need is confirmed and first draft of business case reviewed for a few indications.

"If it [the repositioning project] does not fly from start we [clinical program department] will never get in contact with it". - Clinical Program Manager

The time frame of the clinical programs depend on time for patient recruitment (incidence of the disease, regional distribution of patients, the overall possibility to find patients), but also the treatment time (how long the study have to continue to show results). A change from a chronic disease to a periodic disease will also have impact on the study length. As a periodic usage of the drug could trigger a production of antibodies against the drug, longer clinical studies to confirm efficacy and safety would be needed. The price depend on the number of patients and how long period the patient have to be hospitalized, or more exact, the number of patient visits. The number of studies will also affect the time and cost. A third important factor for the success of the clinical programs is how well validated the end-points are. In larger indications the regulatory authorities have guidelines for these end-points. As smaller indications often lack these end-point guidelines the risk of failing increases. To decrease this risk, the Clinical Program Leader stresses the importance of studying other companies that have conducted clinical studies in the same patient population to learn from their success and failures.

Every clinical study will compare the developed drug to another treatment option. This comparison treatment will differ from country to country. Some demand a comparison with the product that is currently used for the indication, off-label or not. Other countries demand a comparison between the new product and the product that is approved for that specific indication, despite if it is used or not. A third option is a comparison only against placebo or against not doing anything. This will affect both the cost of the study and the threshold to approval.

"Many companies aim to go directly to Phase III, skipping Phase II, by using supplementary data from ISS studies and publications. But Phase II is very important in order to assure the right end-points, subpopulation, dosage, and follow-up-time, which is needed to succeed with a Phase III study." - Clinical Program Leader

Pricing

Something that cannot be overlooked for the business case is pricing and pricing opportunities. What differs from other industries is that price on pharmaceuticals is decided through price and reimbursement negotiations with payers right after a regulatory market approval. Just like regulatory systems, pricing differs from country to country. In Europe, the price is decided in relation to other optional treatments available, their cost, efficacy, and safety. Or, as the Global Director Health Outcomes puts it: *"What is the cost of not receiving our treatment?"*. In Germany an immediate market access is given where sales are made at the suggested price until authorities have decided upon their reimbursement. In other European countries as well as in Japan and Canada, you may not sell until the negotiations are done, which could take from six month up to several years. The United States has a different pricing system, where the price is negotiated freely with insurance companies. As in Germany, you will get immediate access to market. This difference between the North American and the European market has resulted in the price for Zepophan to decrease in Europe while it increases in the United States.

"Pricing is only one element in the repositioning story, but it might change the business case substantially." – External Affairs and Patient Access

The case of repositioning becomes complex since the product already has a price. By expanding to a new indication the company has to go through the process of price acceptance and reimbursement but with the downside of already having a price. As prices normally do not increase this only means a great risk of getting a price-cut, which also follows the natural cause of "increased volume, decreased price". To make the story even more complex, several European countries follow a reference pricing system. In other words, they base their pricing on the price in other countries (such as country of origin, UK or a combination of several countries) resulting in a domino-effect if the price decreases at one market.

"As soon as the price is reviewed, they [payers] take the opportunity to lower the price even though we present a better product. This has happen foremost in countries with poor economy such as France and Italy. In the United States the situation is different where the price increases from year to year due to their free pricing." - Regulatory Affairs Manager II

"One commonly tries to get access to the market with highest product price first, since the price only decreases with a larger target population" - Nordic Patient Access Lead

Zepophan was developed for a large indication with several available treatments, to later be used foremost in rare indications. This resulted in a price not reflecting the actual value of the treatment. Hence, the product already has constrained margins and a price-cut could jeopordize the business case.

"The price is suppose to correspond to the effect, but that is not quite the case for Zepophan." - Global Director Health Outcomes

"The greatest challenge in this case must be the price. Since we start at a fairly low level that we will not be able to increase, that is probably what will cause the show stopper." - Nordic Patient Access Lead

There are ways to increase the price. One is to withdraw the product from the larger indication before launching it for the smaller indication with high unmet medical need. Another is to launch the product as a new brand. There are, however, constraints with these options. A withdrawal of the product from the big indication would limit the access to the drug for those critically ill patients receiving the drug as a third line treatment today. It is also difficult to change the price without changing the product. It would be unethical to sell the same product with a new brand name at a higher price, and as long as the lower priced drug can be used you cannot hinder physicians to prescribe that drug instead. Hence, a more extreme change in the product, such as a new dosage, would be needed in order to prevent substitute use of the old product.

"One can consider a re-branding in conjunction with a repositioning. In the case of Zepophan such branding would be possible in a new, orphan indication where there are no overlapping patients with the first, bigger indication." - Product Group Manager

"Most likely you will not be able to change the price." – Global HEOR & Country Patient Access

5.1.3 Scientific support

When making a decision on whether to reposition into a new indication or not all interviewees mentioned the importance of available data, data that can show the drugs efficacy in a specific indication. Such data is often received from external investigator sponsored studies (ISS) or publications. In the next step the company conducts own clinical studies to confirm the drugs efficacy, prove its safety and to define the target patient group.

As in many other repositioning cases, Zepophan has the regulatory package with safety, toxicity and efficacy data which minimizes the extra work that has to be done before receiving an approval in a new indication with the same mechanism of action. If the new indication is related to the old one more data can be used from the already approved studies. This data, in combination with ISS and publications, can work supportive and allow for smaller studies or even give an approval without a clinical study. The latter may happen in the EMENAR countries (Europe, Middle East, North Africa and Russia), while the FDA require raw data produced by the company to assure that the study has been performed according to certain quality standards before giving an approval. Objective study data is also valuable as a neutralizing factor to the often subjective view of clinical experts, especially in small indication where the uncertainty is greater.

"If all other factors are the same but one indication show lower risk it will be advantageous. For example, having ISSs that we can use would give an overall lower risk." - Clinical Program Manager

"The less we guess the better." - Product Group Manager

Scientific Rationale

Knowledge about the scientific rational was also highly valued within the R&D section, but was also mentioned by the Clinical Study and Regulatory Affairs representatives. The Principal Scientist suggested that having the scientific rationale proven could influence the choice of indication.

"With my R&D background I would look at the scientific rational, after the medical need is determined and before looking into the commercial parameters." - Senior Director Biomedical Science

"If you have a clear scientific rationale and a medical need then it almost feels like a dereliction of duty not to try to do something." - Principal Scientist

The rational should, according to the Regulatory Affairs Manager I, be confirmed by a biomarker or animal model in a pre-clinical study or ISS before presenting the case to the FDA for Scientific Advice.

5.1.4 Timing

Another parameter to reflect over is the timing of the repositioning. To find a good moment where the company best can combine resources and opportunities is important. Expanding to a new indication will also affect the supply and the company has to make sure that they can cover a larger population and assure customer access to the product. As the Global Director Health Outcomes explained it, the company have all alternatives from not doing any investments to choose to invest in a couple of indications.

"We know that Zepophan functions well, has a good safety profile, there is a medical need and we have experts. Therefor the risk is kind of low. But, on the other hand, a repositioning still requires extensive resources in order to receive an approval. So the question is what we have power to do today." - Regulatory Affairs Manager II

As the Nordic Patient Access Lead saw the situation, it might not be worth repositioning into a new indication since the cost of market approval and price negotiations is high and what is earned from off-label sales today might be enough. On the other hand, there is an image aspect of providing better treatment access to the patients. From a regulatory perspective the Regulatory Affairs Manager II saw an issue to have a product that is approved in one area but mostly used in other indications, off-label. Since USA and some countries in EU only give reimbursement to approved indications the physicians subscribes the medicine as for the approved indication while it is actually used in a non-approved indication. This causes safety issues where side effects are reported for the approved indication where the drug actually was used in another indication. Hence, the regulatory authorities encourage Zepo to seek approval in the indications where Zepophan is used off-label.

"Emotions may also affect the decision - people who have worked with an indication for a long time tend to want to push things forward, but if you look at it purely economic, it is perhaps not the best for the company." - Global Director Health Outcomes

"Sometimes it may not be worth registration for a new indication since the income from named patent use is good." - Regulatory Affairs Manager I

Another concern that was brought up by some of the interviewees was how a new indication could influence the existing indications. Since a extension equals a larger target population the prices could drop at the existing markets. Some markets are not possible to enter since the development cost risk to exceed the income from sales (referring to areas where Zepophan is sold at a cheaper price). Further any safety issue in a new indication would threaten the total global sale since side effects are commonly connected to a drug rather than an indication. Hence, before entering a new market it has to be proven to be safe.

"We have to look at what will happen with the indications we already have. Any safety changes or large negative impact on price that affects the other indications would indicate a big 'no-no' for me." - Clinical Program Leader

Competition

The competition should also be considered for each indication, both current and future. Competitors may be products having the same mechanism of action, same indication target and/or same target population.

Most would argue that being the first alternative treatment is important, especially in small target markets such as in orphan indications. One way of being the first alternative is being the first drug at the market as the only-choice brand, another alternative is being the best choice from a safety, efficacy, convenience, and price perspective.

There are pros and cons of being first to market. An attractive feature of being first is that the unmet need is big which eases the approval process and clinicians are more eager to give patients access to the drug. These products also tend to get high loyalty from patients. However, the Clinical Program Leader saw the upside of not coming as number one to a new indication. Coming as number two or three into a new, unknown, area can be advantageous since the knowledge learned by the competitor's clinical studies can be used to avoid pitfalls. The VP Global Brands also mentioned how the competitors could develop the market and educate clinicians in the field. But then, the company has to show a clear differentiated positioning to attract customers and one should also calculate on fewer market shares as number two and consider if it still is worth the repositioning. Another risk of coming second is that patients may not be as willing to take part of the studies since a treatment already exists, this would prolong the development times.

The competitors may have different administration routs, longer half-life, and other price strategies. This means that Zepophan can be more or less appropriate in comparison to competitors. Competitors will enter the market, but what advantages they will show compared to Zepophan is not known, nor is their pricing strategy. The current immediate competitors have much higher price than Zepophan. Meaning that Zepophan still will be used in some areas where the competitor would be more suitable, due to budget constrains.

Future competition consists of other drugs, biosimilars, but also products in Zepo's own pipeline. As the approval can be both faster and cheaper if there are no other treatments available, an indication could be left out of the repositioning to be saved to the next generation drugs coming in pipeline. An other strategy would be to use this repositioning process to prepare the market for the next-coming molecule.

If Zepophan works in a new indication the chance is good that also next generation molecule will have effect in that indication. Hence, by considering what could be interesting for the next generation molecule the company can take advantage of the development and clinical efforts a repositioning requires as well as building relationships with treating physicians.

"We do not want to cannibalize on our own future markets." - Senior Director Biomedical Science

"We have the next generation Zepophan in pipeline and therefor it is important to also consider the long term results from a repositioning. - Regulatory Affairs Manager II

For the case studied in this thesis, the VP Global Brands stressed the importance of reaching the new market-indication fast in combination with a reasonable investment. At the same time the additional production volume and revenue from the repositioning should be small enough, not to attract biosimilar competitors. To protect the product from competitors it is important to strengthen its position to ensure that clinicians choose Zepophan over other products.

"The biosimilar market is fairly new and as long as our total revenue is not too big we hope to stay out of the radar of biosimilars which have focus on larger target markets. We also have other products in our pipeline with a potential future that we do not want to harm." - VP Global Brands

"My main concern is biosimilars, that we give away a new indication to biosimilar companies and that our price is too low to give any income from an orphan indication. It feels like the business case is not there." - Nordic Patient Access Lead

Moreover, competition can be other than market competition. Other competition that should be considered are competitors working with the same patient group (not necessary the same disease). Such competition will minimize the access to patients for clinical studies.

5.1.5 Life cycle extenders

Main focus in the product life cycle management is to efficiently utilize the potential of a product during its life time in order to create value to the company. The longer the lifetime is, the more value can be extracted from the product. Prolonging the lifetime of a pharmaceutical product was also discussed during the interviews. Giving extra time at the market with barriers against cheaper copies of the product, generics or biosimilars, can be done through finding new patents to protect the product or by receiving an orphan designation. These two will be discussed now.

Patent

Zepophan is getting closer to the global patent cliff. This was a main concern mentioned by the majority of the interviewees. In this situation it is valuable to find ways of prolonging its life time and evaluate the upcoming risks.

One can normally receive a patent for an in-use-patent for a new indication, but in the case of a planned-match repositioning where academics or clinical groups prove the efficacy of the drug in a new indication, the patent right (if any) is theirs.

"If we can get a patent it would make a big difference." - Nordic Patient Access Lead

"It is now or never for Zepophan." - Regulatory Affairs Manager II

Changes in the formulation will not protect the molecule and hence, will not affect the threat from biosimilars. Such change will however increase the attractiveness to the users. If the company cannot protect their molecule with a patent the repositioning investments may go to waste. A biosimilar could conduct a small study in one indication to prove its similarities with the original drug and then sell on all markets where the original drug is approved. Larger companies with strong marketing and distribution channels could easily take Zepo's position. To minimize this threat the VP Global Brands stressed the importance of staying out of radar of the biosimilars by avoiding larger markets.

Orphan designation

Receiving and orphan designation from the regulatory authorities provides with a market exclusivity of seven to ten years and is therefore another alternative for extending the life cycle of the drug. An orphan designation will also give other advantages such as allowing for smaller and fewer clinical studies than for regular indications. Two interdependent studies are usually required but in the case of a rare disease one can argue for only conducting one study since the number of patients are few and instead supportive data from ISS and publications are used as complement. Further, an orphan designation will also give faster review times to approval (only 6 month compared to 12, normally) and eliminated application fees.

A drawbacks, in Europe, is that an orphan designation requires a new brand with a new package for the product at the orphan market. This is a quite big cost for the supply department. Due to this, some indications are not worth seeking orphan designation for, since the incentives such as market exclusivity do not overweight this cost in a small market, especially when the market is not big enough to attract.

"A market exclusivity may protect the space around the indication but not the molecule. Anyone can make a biosimilar." - Regulatory Affairs Manager II

5.1.6 External relations

This is a broad subject covering several different external relations that are necessary to maintain in order to succeed with a repositioning initiative. These are relations with: clinicians and academics, patients, regulatory authorities, payers, and business partners.

"We can not possibly have all competence necessary in-house." - Clinical Program Manager

Clinicians and academics

Discussed by all interviewees was the relationship with treating clinicians and academic experts with the common conception of seeing this relationship as vital but complicated.

"This relationship [with treating physicians], and the quality of it, can be decisive if choosing between two alternatives with equal medical need and medical effect." - Principal Scientist

"Knowing the physicians will enable receiving information as well as ease the distribution." - VP Global Brand

First of all, it is the treating clinicians that, through off-label or named patient use, has showed the efficacy of Zepophan in new indications. These are the Key Opinion Leaders (KOLs) that know the product and the market since they are the ones actually meeting the patients to see their need. Keeping a good relationship with experts in the field, clinicians and academics, will help guide the company through new and unknown areas of diseases. In turn, it will enable shaping the product and the clinical programs to fit the end target group. They also have an important role in spreading the word about the product in non-approved indications, where company driven marketing is not allowed.

"If we have talked to a sufficient amount of experts and patients, and designed a good clinical program, the chance is high that we would get an approval." - Global Regulatory Affairs Manager

Further, clinicians also have to show commitment to perform clinical studies. This willingness often depend on the medical need but also on the relationship. Some specialists in certain areas are more eager to find new treatments than in other areas, especially in cases where alternative treatments are scarce and the amount of new study proposals few.

As part of the relationship the company has to motivate and educate the clinical force. The cost of such information will depend on the size of the group. This information and communication is also important since authorities ask experts what they think of the presented data, if they see a need for the product, and what efficacy they would like to see. Hence, the relationship may help the product to approval.

Patient access

One of the more critical points in the repositioning process is, according to the Clinical Program Manager, the patient recruitment process for clinical studies. Patients move, declines the offer, suffer from another conflicting disease or show instability with current treatment which prevent them from participating in the study. This results in an insufficient amount of study data and may lead to rejection of the approval application. Another important aspect of the patient relation is the essential of understanding the actual customer need.

"Sometimes a particular symptom can be more limiting than the disease it self." - Regulatory Affairs Manager II

A good relation with patients is therefor crucial in order to facilitate the coordination of necessary clinical programs. Such relation is often enabled through the group of treating clinicians or patient organizations which is an important channel giving valuable connections to patients and their families.

Regulatory authorities

Another relationship that has to be treated with care is the relationship with the regulatory authorities. These are the instance in charge of the drug approval. Chances of approval will increase if the company seeks advice from the regulatory authorities early in the process. It starts with a Scientific Advice to get their approval and opinion on the clinical program plan. Sometimes they will require a specific type of study, which is good to be aware of before starting the expensive studies.

"A second critical point is the communication and agreements with regulatory authorities. What are their demands? Are they doable?" - Clinical Program Manager

For Zepo this includes relationships with the FDA (the U.S. Food and Drug Administration) and EMA (European Medicines Agency), as USA and Europe are the main markets for the company. Demands given by the FDA and EMA are relatively predictable since they follow a number of rules and guidelines. However, Zepo also have to communicate with local authorities of the EMENAR countries. Demands from these tend to be more unpredictable (especially in EMENAR countries outside of Europe) which may result in a business case starting out as positive, will end up being a loosing affair.

"It is a jungle to understand the different countries and you may get one answer the first day and another answer the second day." - Regulatory Affairs Manager I

"They [local authorities] might even take out special fees or a percent of the total sales." - Regulatory Affairs Manager II

The relation to care extra for is the relationship with the FDA since an approval from the FDA most probably will have positive effect on approval in other regions as well. This is known among physicians and the drug will get an unofficial quality approval which also may lead to an increased off-label sale in other regions.

Payers

Traditionally, pharmaceutical companies have striven for an approval from the regulatory authorities only. However, today, the pricing authorities are demanding as much information as the regulatory authorities. If the company cannot show statistically proved data on the medical and clinical benefit as well as the socioeconomic advantage of the drug they may end up with a market approved drug that can not be sold since it lacks price-approval. Hence, it has become more important to also care for the relationship with the price authorities.

"Usually the pricing authorities have other demands than regulatory authorities have. This results in approved dugs that cannot be sold since the price is not accepted." - Clinical Program Leader

"It is not always easy for us. We have a strategy but when we come to submitting a pricing and reimbursement negotiation the authority thinks differently." – Global HEOR & Country Patient Access

If the company extends the market with an additional indication there is a risk of price reduction, despite if the drug is improved or not. It is therefor, as the Product Group Manager explained, crucial to involve payers early on in the decision process to see their willingness to pay in each region. Pricing in the United States is free which means that the company can increase their prices. In this situation it is particularly important to care about the relations. A chock-increase of price will definitely influence the payers attitude towards future collaborations with the company.

Business partners

Some repositioning initiatives would require an external business partner, as in the case where Zepo for example lacks resources or experience of that specific treatment area. Such partnerships may be limiting, especially in small indications, as a big part of the revenue will go to the partner.

"Our partners tend to take their share." - Regulatory Affairs Manager II

Despite revenue loss, Zepo values the possibility to partnership and is now part of a EU program called FP7. This program aim to stimulate research of rare diseases through collaborations amongst patient groups, clinicians and industry. In this case the product is developed off-patent, meaning that despite large investments there will not be any protection against generica when the drug reaches the market. VP Global Brands explains that such business, only generating economic loss, still is interesting in order for the company to learn and become better at collaborating with external actors.

5.2 Grading parameters

As a complement to the comments made during the interviews all respondents took some minutes to grade a number of parameters in a grading-list. These parameters were parameters that had earlier been used by employees at the company during repositioning, which was summarized during the pre-study. Since the interviews covered more and sometimes slightly different themes than the original parameters all parameters presented above are not represented in Table 5.1. In order to grade the additional parameters, literature and qualitative data from the empirical material were used.

Each interviewee was asked to grade the parameters after how important they are when considering a repositioning opportunity. Respective number from 1 to 5 represents "not important", "niether important nor unimportant", "quite important", "important" and "very important", in that order. The summary is presented in Table 5.1 below.

The response rate to each parameter was fairly low, foremost due to the interviewees finding it difficult to grade one parameter as more important than another, as the parameters interact and affect each other. For example, product changes will become important if the competition is tough, if not it does not matter if the product is given intravenous or subcutaneous as long as it treats the patient. Further, having an orphan indication would not by itself be important but it may influence the market parameters, effecting time to market and market exclusivity. For the Nordic Patient Access Lead a mechanism evidence and an optimal half-life was by themselves "not important" but if they had influence on efficacy it became "very important". Another comment made was that it is valuable to know the prevalence but the number does not necessary have to be large.

In summary, the medical need received the highest grading from most of the interviewees, followed by an evidence of the mechanism. Having the patient group located in the United States was also considered as "important" to "very important" by the majority of the respondents and so was the pricing. The lowest score was given to having a business partner for the repositioning process. This was not scored low as in "it does not matter", but rather followed by comments like "rather us than a partner", "partnerships are hard", or "a partner would take the profit".

A short analysis of each competence area (Research and Development, Clinical Studies, Regulatory, Pricing and Commercial) show some differences. Looking at the competition you may see the natural shifting of seeing the future competition as more important than the current further back in the product chain, namely among the commercial respondents. For the commercial representatives, time to market was also highly valued, and hence also those parameters helping with that, such as an orphan designation. While one person from commercial argued that "everything shortening the way to market is good", the other one scored treating physicians as "important" since they can have great influence in the up-take of

the product. It would also be preferable if the group of treating physicians was not too large, according to the VP Global Brands, since Zepo is a fairly small company that would not afford to educate a larger group of clinicians.

The pricing representatives had very shifting answers on the importance of the number of patients as well of the importance of the clinical costs. As the Global HEOR & Country Patient Access put it, all products go through a clinical development and regulatory approval before it can be launched, the cost of clinical program is going to be about the same for all alternatives.

The representatives from regulatory were more coherent in their answers and valued the clinical program cost and time high. One argument was that a large cost of the clinical program may kill the business case. Further, the time was important since the patent cliff is approaching and a repositioning should preferably be performed before that happens in order to recoup the extra expenses.

Neither did the clinical study respondents have a very different view compared to other groups. A comment to the total cost of the clinical programs was that a million SEK cheaper will not affect the choice. Moreover, any data supporting pricing was valued high by the interviewees working with pricing of the case-product.

5.3 Summary of the empirical findings

This chapter presented six main categories that were identified during the conducted interviews. The first was a *medical need* which was considered to be the most important parameter to consider before a repositioning. A large unmet medical need will ease both pricing and regulatory approval as well as the market uptake of the product. Further, the importance of a well defined subpopulation was also discussed in order to show efficacy and increase the chances of regulatory and pricing approval. Next category was the *economic return* which depend on both, development, clinical studies and pricing. Other important categories to consider before a repositioning were *scientific support*, *timing*, *life cycle extenders* such as patent and orphan designation, and *external relations*. Moreover, a regular repositioning was considered to be safer than a repositioning aided by reformulation since less risky investments has to be made.

By grading a set of parameters the interviewees also show the importance of having a market in the United States where the pricing opportunities are better than in Europe. The scores also show Zepo's desire to perform a repositioning without any business partnership.

Table 5.1: Grading parameters, a summary from the interviews

Parameter	Research and Development		Clinical Studies		Regulatory			Pricing				Commercial		Avarage score
Incidence		3	5			3	3		4		5	4		2.07
Prevalence		3	5		4	3	3		4		5	4		2.38
Patients US		5	5		5	3	4	4	1	5	2	5	5	3.38
Patients EMENAR		2	5		4	3	4	4	1	5	2	4		2.61
Patients tot		4	5			3	3		1		5	4		1.92
Treatment frequency		3	3			3	4	3	5		4	3		2.15
Syringes per year		4	5		4	3	3		5		5	3		2.46
Market segment		3	4			3	3		2		4	5		1.84
Current competition		4	4			4	4	4	5	5	4	3		2.84
Future competition		4	4			4	4	4	4	3	5	5	4	3.15
Mechanism evidence	4	4	5	4	5	4	4		5		4	5	5	3.76
Optimal half-life	3	3	4				3		5		5	2		1.92
IV or SC	3	3	5				3	2	4	2	4	1		2.07
Target product attribute	4	3	4				5		5	5	5	2		2.53
ISS or Publication	4	4	4	4	3	4	4		3	5	5	3		3.30
Completed clinical program	3	2	3	4		5	4		3	5	5	3		2.84
Clinical program cost	4	5	3			4	4	4	1	5	1	4		2.69
Clinical Program time	4	4	4			5	5	4	1	4	5	4		3.07
Medical need	5	4	5	5		4	5	5	5	5	5	4		4.00
Orphan drug	2	3	2			3	2	3	5		2	5	5	2.46
Pricing		4			4	4	5	4	5	5	5	3	5	3.38
Geography	2	4	5		4	3	3		2		4	3		2.30
Sobi/Partner		3	1			2	3		1	3	1	5		1.46
Treating physicians		4	5			2	5	3	1		5	2	4	2.38

Chapter 6

Ranking opportunities - a strategic repositioning model

An analysis of the findings presented in the previous chapter (the found parameters and the grading of the same), in combination with literature, resulted in a relative weighting of the parameters. This in turn served as a basis for a repositioning model that may be used when choosing between several repositioning opportunities. This is presented in this chapter.

"A company has to balance all these parameters and make a decision on what is the best thing to do, it is not so easy". – External Affairs and Patient Access

"There are no easy answers, one has to weighing the information we have." - Global Director Health Outcomes

"When looking at the options this early in the process one can find plenty of factors and it can be one of the smaller factors that show to have greatest impact on the cost for patients or healthcare." - Nordic Patient Access Lead

"It sounds quite easy but the big question is; What factors should we take into consideration?" - Product Group Manager

"There are many small pieces of the puzzle and it might be different puzzle pieces in different projects." - VP Global Brands

6.1 Three parameter priority groups

Although all these parameters presented in the previous chapter are important in order for the repositioning process to be successful there are some parameters that are vital while others are not. I call these primary, secondary and tertiary parameters. If any of the primary parameters are not fulfilled the repositioning is deemed to fail. Hence, it is logical to first check the boxes of these parameters in a go/no-go decision flowchart, followed by a weighting of the secondary parameters to mutually rank the remaining repositioning opportunities. If the amount of repositioning options are still too many the third step would be to look at how well the options comply with the business strategy.

To determine which parameters that are more important than others I have used repositioning literature, qualitative data from interviews as well as the grading made by each interviewee.

6.1.1 Primary Parameters

A repositioning initiative, as defined in this thesis, aims to reuse a marketed drug in a new indication. By looking at the process it is clear that to make this possible you must first of all have a drug and a receptive target market (indication), in the next step the drug has to get an approval from the regulatory and pricing authorities in order to reach the new market as a repositioned drug. These are defined as the

primary parameters for a repositioning process. Further, this process could either lead to a successful repositioning with a good return on investment or it may be a loosing deal for the company. Factors affecting this outcome will be defined as secondary parameters and are presented in the next section below.

Going back to the primary parameters, we have: (1) a marketed drug, (2) a receptive target-indication, (3) regulatory approval, and (4) pricing approval. If any of these parameters are missing there will not be a repositioning case. The first parameter is in this case given, Zepophan, but can also be assumed to be given for the general repositioning case. The following parameters will now be presented one at a time.

A receptive target-indication

For a target-indication to be receptive there has to exist a need for treatment and the drug used for repositioning must work. The need is defined by the *medical need* which has to be confirmed. If there is no urgent need the chances for approval and sales are small. The medical need was also marked as "important" to "very important" by all interviewees responding to that parameter in the grading list. Entering an indication with a high unmet medical need will further always be valuable from a socioeconomic perspective even through the business case is negative.

An unmet medical need is one thing, but then the drug also has to work in order to satisfy that need. This in turn is defined by the *scientific rational* which can be confirmed by any data available such as ISS, publications or in-house research. The scientific rational *per se* was valued as "important" to "very important" by all responding interviewees but one, whom graded the scientific rational as "not important" with the comment: "as long as it works". In conclusion it did not matter how this scientific rational was confirmed but it should be confirmed before doing any further investment.

Lastly, defining the *subpopulation* that will respond to the drug is crucial in order for the drug to show superior efficacy in the indication with an unmet medical need. The subpopulation was mentioned during the interviews as being very important but was not evaluated by the grading questionnaire.

If these three, (1) an unmet medical need, (2) the scientific rationale, and (3) the subpopulation, are confirmed the box for the parameter "receptive target indication" can be checked and a go-decision can be made. If any of the above subcategories are missing, more studies are required before a go-decision can be made.

Regulatory approval

To receive a regulatory approval the drug has to pass the clinical studies. One can never know for sure if the drug will pass the clinical studies but if it at this stage of the repositioning decision is shown that one of the indications is likely to fail it can preferably be rejected early in a no-go decision. What can be considered in the regulatory approval is the *size of the target population* and the *geographic distribution*. If it is going to be hard to gather a big enough patient group to perform the studies, the indication might as well be rejected. The graded evaluation of the population size differed greatly from "not important" to "very important". The geographic distribution was considered as more important, foremost due to the business case as will be presented under the secondary parameters, but also from a regulatory perspective.

The outcome of the regulatory approval will further depend on how well *validated end-points* there are. These end-points are commonly described in guidelines by the regulatory authorities for larger indications. Hence smaller indications are more risky. If any other company have performed a clinical program one can learn from that. If not, there is no reason to give a no-go decision but one should be aware of the increased risk of failure.

Pricing approval

The company has to assure that they first of all will get a price approval for their product in the new indication and secondly that the increased size of the market will justify a slight decrease of the price which is most probably going to happen. The larger new patient group you have, the more will the price decrease. This latter will however be more discussed as a secondary parameter affecting the outcome of the business case.

However, pricing is closely linked to the medical need as the price is decided in relation to other *optional treatments*. But also if the drug used for repositioning can *decrease other costs* associated with hospitalization of the patients.

The primary parameters are illustrated in Figure 6.1. When these parameters are confirmed the next step is to see how positive the business case can be and consider the coherence with the overall business strategy. As can be seen above, the regulatory approval will benefit from a not too small target indication while the the pricing would benefit from a not too large indication. Hence, a balance between a not too small and not too large target indication is desired. The first of the primary parameters, a receptive target-indication, can be fairly well evaluated as fulfilled or not. The following parameters however, the regulatory and pricing approval, should only be evaluated as a no-go decision if there are any clear signs that an approval is not likely to happen.

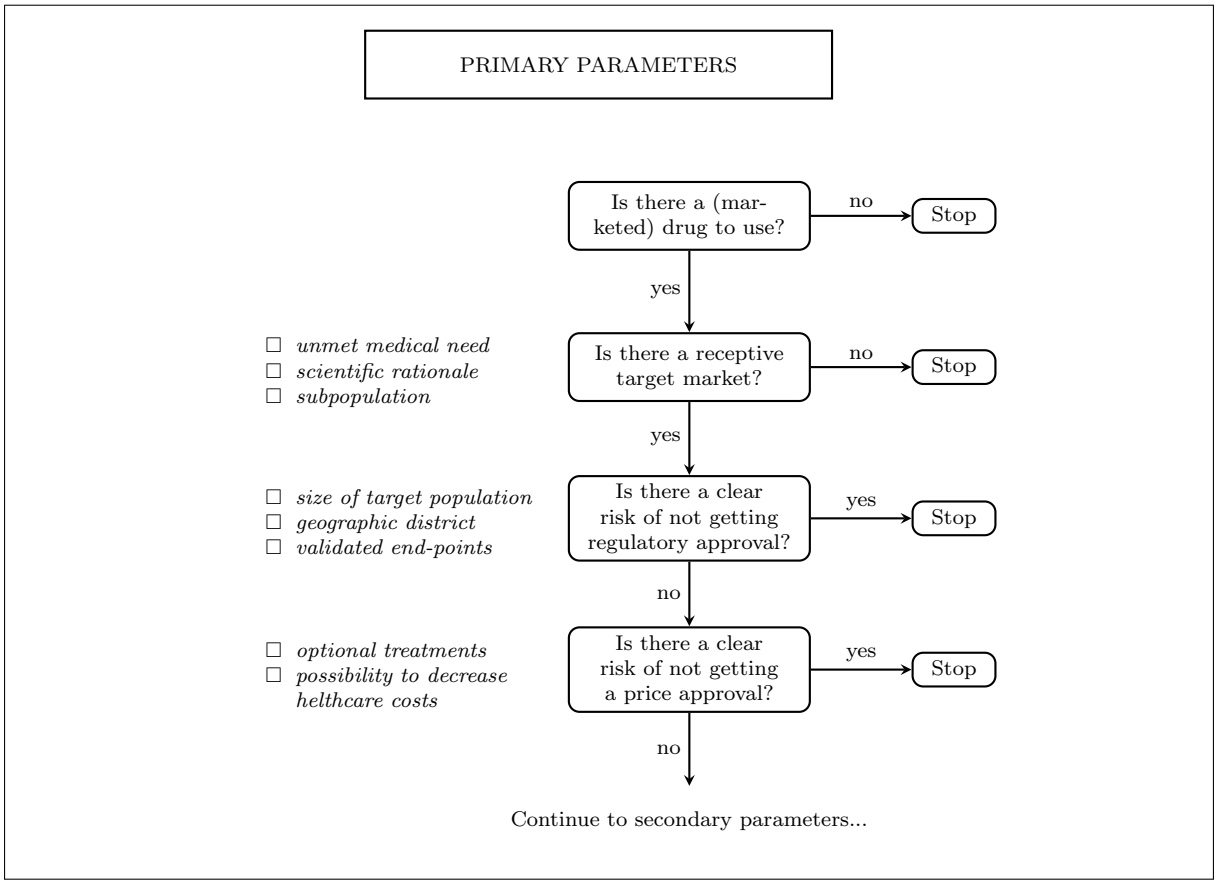


Figure 6.1: Primary parameters in the three-step repositioning model

6.1.2 Secondary Parameters

As the VP Global Brands said, repositioning is an iterative process where more and more solid data is collected after each run. Since companies have a limited amount of resources, it is important to be able to separate repositioning propositions that have potential from those that have not, with relatively small and simple means. Hence, after confirming the primary parameters, it is time to evaluate an approximate potential of each repositioning proposition, eliminating poor alternatives. In the second and third iteration the company will make the business cases of the best potential alternatives more solid, before going to FDA for a Scientific Advice.

Weighting the secondary parameters will therefor result in a ranking of the parameters in terms of how much potential at low risk each proposed indication has. But before going to the weighting, the secondary parameters will be presented, in no particular order, here below.

Assuming that the goal of a repositioning is to get a positive economic return to the company, then the business case depend on the investments that may be necessary in order to reach the target market and what economical return the new market can be expected to give, as well as how fast positive economic

results can be shown. This gives us three main parameters: (1) total cost to launch, (2) total income from sales, and (3) time to income.

Total cost to launch

The greatest costs in the repositioning process are the *development* costs (if any) and the costs of *clinical studies*. Development costs that have to be considered are changes in the drug in order to better fit the target patient-group in the new indication. This is also called the *target product profile*. Hence, the company have to revise what is more important for the product in order to be attractive to the new target patient. That could be an intravenous administration versus a subcutaneous, a short versus a long half-life of the product, a possible storage at room temperature versus a refrigerated product or a new dosage.

Changes may increase the chances for approval since it can make a product more convenient for the patients than existing products, or decrease the overall cost of health-care. However, changes in the product will also require extra clinical studies to confirm the safety, it will also require longer approval times which will drive the cost. The risk of failure is also larger than a pure repositioning without any reformulation.

A change not coupled to the development, but which will require further safety studies, is a change of going from a daily injection to a *periodic use* of the drug. Such change could trigger the production of antibodies and must be evaluated in clinical studies.

Other factors affecting the cost of clinical studies are the *size of the patient group*, *number of studies required*, *number of treating physicians* and what *product to compare with* in the study. The more patient visits and the longer the patients have to be hospitalized the more expensive will the study be. Required amount of studies will also depend on the size of the target patient group where an orphan designation may have fewer and smaller studies due to the complexity of finding patients. If an orphan indication also means that there are *specialist treatment centers* it will decrease the total cost compared with having patients and physicians spread out over several centers. A large group of clinicians also means a large group to inform and educate which is an additional cost. Moreover, what product that has to be used as comparison in the studies will also have effect on the total cost. If placebo or "not doing anything" works as control the cost will be much lower than if a high cost product should be used as control. This depend on what available treatments there are at the time of the studies.

Total income from sales

Calculating the expected income from sales is complex since it depends on several estimates. However the uncertainty of these estimates will be more or less equal between the potential indications and therefor one can still receive a mutual comparison of the indications.

The total income from sales will depend on primarily the *market size*, *dosage per patient and year*, *competitors*, and potential *price of the product*. A larger population will give a potentially higher income, if the price can be expected not to drop. There are regions with economic constrains and high prevalence of the disease, in such regions you may reach a large group but since the economic strength is missing there is a risk of a price drop. However, one also has to consider any *patient overlap* with current indications. If there are a overlap these patients are already using the drug and there will not be an increase in sales.

Competitors (current and future) must also be considered to enable an estimation of the total market share. This was also something considered to be "important" or "very important" for interviewees within every competence area (research & development, clinical studies, regulatory affairs, pricing, and commercial). One should look at what studies the competitors are doing, what is coming in pipeline and what advantages their products might have. Moreover, the threat from biosimilars is assumed to be higher in indications giving great production volumes and increased revenues, although this biosimilar market is fairly new and hence, rather unpredictable.

Pricing was also touched upon in the primary factors, although it had a focus on getting a price approval in order to get the product to the market. As secondary factor it is all about getting the best price possible to increase the economic income for a product already priced in another indications. In order to increase the price one can either withdraw the product from the previous indication or to launch the product as a new brand. The pros and cons of the alternatives have to be considered such as ethical issues, additional costs, parallel use etc. Further, a price drop is more likely to happen in Europe than in USA where you may see price increases.

By filing for *new patents* or *orphan designation* one can enhance the barriers against competitors, elongating the life of the product and the time period of income. A patent to the molecule can give

protection against biosimilars and other competitors while the orphan designation "only" will give market exclusivity for the new indication. In such attempt one has to consider the cost of these initiatives, such as development costs or re-branding.

Moreover, a *business partnership* will decrease the overall economical return of the investments and should be considered in relation to the economic result.

Time to market

To maximize the return on the product, the time to market is important. *Orphan designation* was mentioned as a factor that may increase the income of the product, it is however also valuable in order to decrease the time to approval in order to faster receive an income on the product. Another factor is the *direct market access* which is applied in some countries (e.g. Germany and United States) while other countries (e.g. Japan and Canada) will not give access until the price is negotiated and approved. This will postpone the income from the product.

The incidence and regional distribution can also be considered along with the treatment time in order to control the *length of the clinical studies*. *Supplementary data* from ISS and publications will also help in minimizing the time used for clinical studies.

Moreover, *external relations* have impact on time to market. Clinicians have an important role, not only in conducting clinical trials, but also for spreading the word about the product. A good relation may hence affect the speed of product acceptance among users. Having patient access is also important in order to get an efficient recruitment of patients to the clinical studies. Communicating with the regulatory authorities and payers will also ease the process and the risk of loosing time due to misunderstandings will decrease.

Another factor that will delay the time to market is any *necessary development* on the product. Depending on the degree of change that may be necessary the research and development will take more or less time.

6.1.3 Weighing of secondary parameters

These secondary parameters are going to be weighted in relation to each other in order to rank the repositioning opportunities to further choose a repositioning opportunity with great potential.

The weighing presented in this sub-section has been inspired by the scoring methods used in the work of Mottley and Newton (1959), Dean and Nishry (1965), and Henriksen and Traynor (1999). Numerical gradings performed by the interviewees in this research study in combination with their qualitative descriptions and support from literature has lead to the weighting presented below. It is not implied to be the ultimate rating. However, as also Mottley and Newton (1959) concludes, the judgment from experts within the process should be satisfactory for rating parameters within their competence area. As interviews has been held with people from five different competence areas, the weighing takes into account the total average score as well as the average score within the competence area connected with the specific parameter. The scores are also compared to the comments made in order to reduce bias due to subjective interpretation of the numbering of 1 to 5.

Each parameter is receiving a weight from 1 to 5, depending on its importance for final repositioning choice. 1 indicates low importance while 5 indicates high importance. Thereafter, the parameter is also given a value of how well the parameter is fulfilled from 0, as not fulfilled, to 5, as fulfilled. The higher number, the more positive is it for the case. Hence, any change that may increase cost and risk while decreasing the economic return will be given a lower number than parameters lowering cost and risk while increasing economic return. In this section the weighing is presented in the figure below. An example of how to use the model with the fulfillment criteria will be presented in the next chapter, *How to use the three-step repositioning model*.

Time to market was valued slightly higher than cost to market, although cost was not unimportant. This is taken into consideration in the weighing. Further, some parameters show a specific relation. An example of such is the "size of patient group" and "dosage per patient and year" within the category of "total income from sales". A large market with few dosages per patient and year could have the same result as a small market with many doses per patient and year. Such relation requires an equal weight for the two factors.

Looking at the development costs, a complicated and expensive change will be weighted as high since it will have great impact on the total cost. This will in later step follow the fulfillment from 0 representing an absolutely necessary change to 5, representing "no change necessary". If there are two options where one requires great and expensive change the total score will be low for that alternative.

Further, if no partnership is needed the case should be ranked high. Hence the partnership will be weighted with a 5 and the fulfillment will be based on the scale from 0 to 5 corresponding to "partnership necessary" to "no partnership needed", respectively.

Table 6.1 summarizes the secondary parameters and their respective weighting.

Table 6.1: Weighing of secondary parameters.

Parameter	Weight	Fulfillment grade
Total cost to launch		
Changes of IV/SC	2	
Change in half-life	2	
Change of dosage	4	
Change to periodic injections	4	
Size of patient group	4	
Number of treating physicians	2	
Price of study-comparison-product	5	
Treatment length	4	
Specialist treatment centers	1	
Total income from sales		
Size of patient group	4	
Dosage per patient and year	3	
Current competitor climate	4	
Future competitor climate	5	
Expected price	5	
New patents	5	
Orphan designation	2	
USA market	5	
Required partnership	5	
Overlapping patient groups	4	
Time to market		
Orphan designation	3	
Direct market access	4	
Supplementary data, ISS/publication	5	
Regional distribution	3	
Required follow-up time	3	
Relation to clinicians	2	
Relation to patients	1	
Necessary development	5	
TOTAL SCORE		

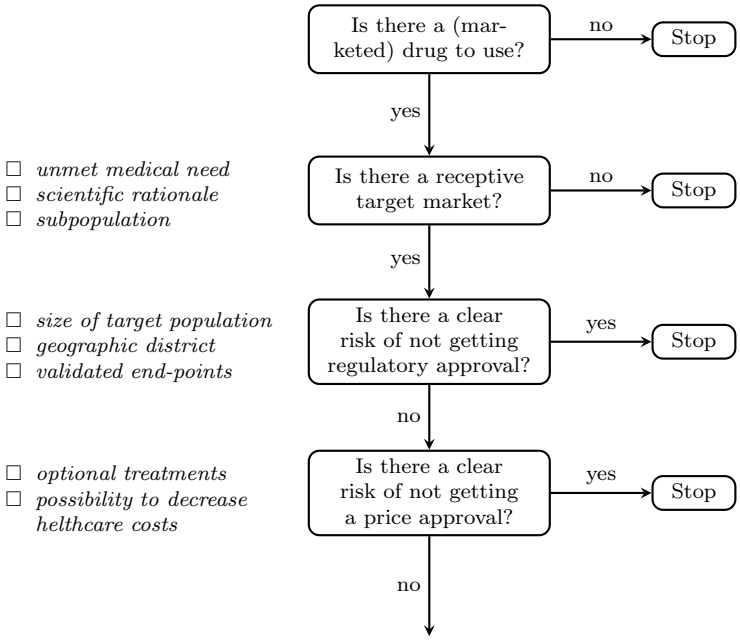
6.1.4 Tertiary parameters

When the primary and secondary parameters have been evaluated and the number of potential indications still has to be reduced one can turn to the tertiary parameters. These parameters will evaluate what alternatives that fit the company strategy best. Factors to consider here are e.g. *pipeline strategies*, *company mission*, and *brand strategies* at a company or product level.

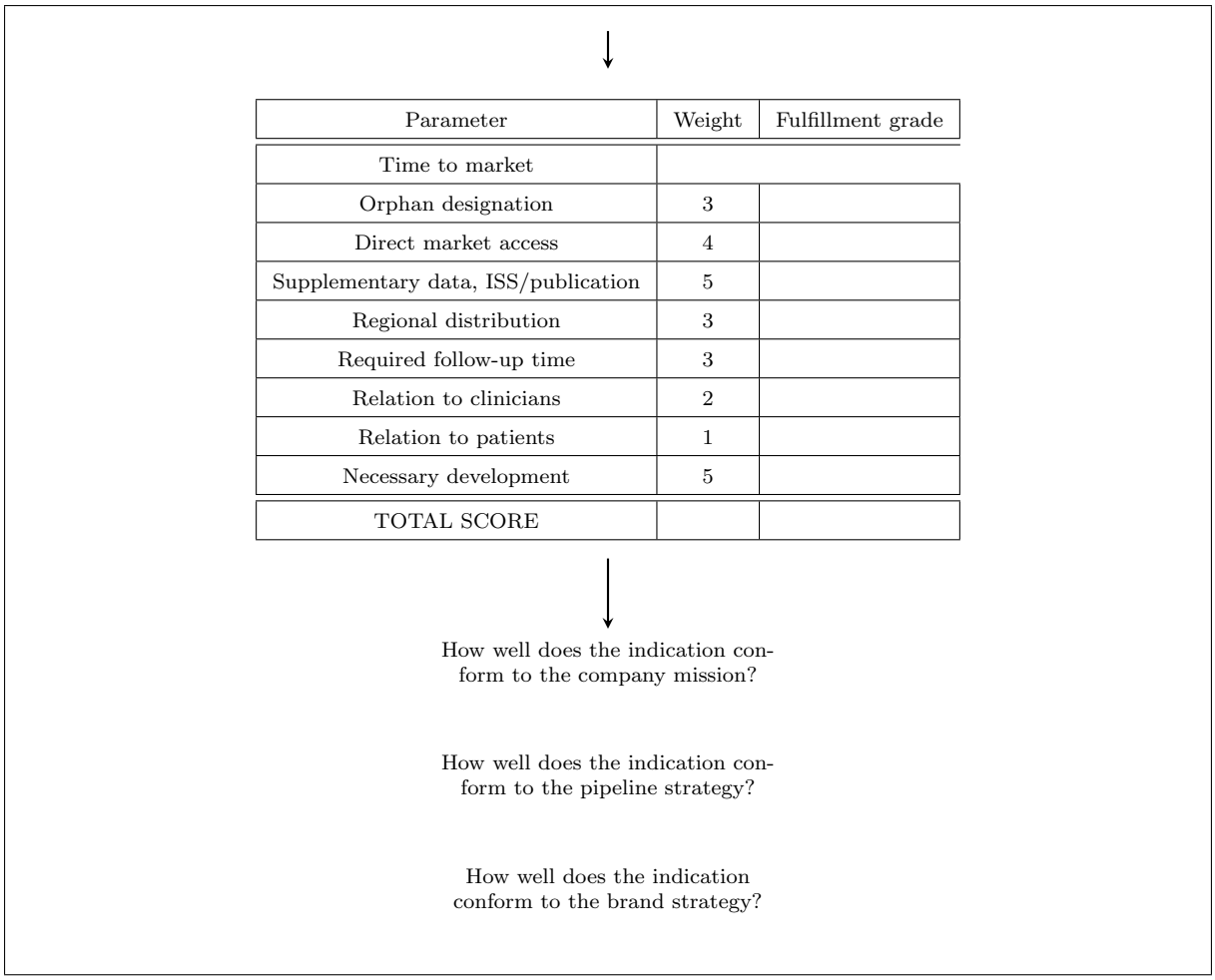
6.2 The three-step repositioning model

From empirics collected through interviews with experienced employees involved in the repositioning process key parameters to be considered in the evaluation of a repositioning opportunity were identified. Data collected during the case study and repositioning literature have further guided me in weighing these parameters in relation to each other. This has resulted in a repositioning model (as can be seen in figure 6.2). The model is a combination of a go/no-go flowchart and a ranking matrix with focus on profitability and medical impact.

THREE-STEP REPOSITIONING MODEL



Parameter	Weight	Fulfillment grade
Total cost to launch		
Changes of IV/SC	2	
Change in half-life	2	
Change of dosage	4	
Change to periodic injections	4	
Size of patient group	4	
Number of treating physicians	2	
Price of study-comparison-product	5	
Treatment length	4	
Specialist treatment centers	1	
Total income from sales		
Size of patient group	4	
Dosage per patient and year	3	
Current competitor climate	4	
Future competitor climate	5	
Expected price	5	
New patents	5	
Orphan designation	2	
USA market	5	
Required partnership	5	
Overlapping patient groups	4	



Parameter	Weight	Fulfillment grade
Time to market		
Orphan designation	3	
Direct market access	4	
Supplementary data, ISS/publication	5	
Regional distribution	3	
Required follow-up time	3	
Relation to clinicians	2	
Relation to patients	1	
Necessary development	5	
TOTAL SCORE		

Figure 6.2: The three-step repositioning model

Chapter 7

How to use the three-step repositioning model

The purpose of this master thesis was to develop a repositioning model in order for pharmaceutical companies to compare different repositioning opportunities. To show the function of this three-step repositioning model it will in this chapter be applied to the case of Zepophan and the three potential repositioning indications studied during the time of writing this thesis.

7.1 Evaluation of primary parameters

The first step will be to consider the primary parameters for each indication. From the given result we may make a go or no-go decision on whether to continue or not with the indication into the second step of the three-step repositioning model. All indications will be considered as a repositioning opportunity with Zepophan, hence the first go/no-go decision will give an approval to continue to look at the receptiveness of the target indication.

The final result of all three indications will be presented in Table 7.2, while the descriptive text follows the process of evaluating Indication A. Data in Table 7.1 presents the indications in their shortest form. Data for this table of indication evaluation was collected from secondary sources such as scientific papers, completed and ongoing clinical case studies and through correspondence with experts during the market and technological analysis. A more detailed presentation of each indication can be found in Appendix C.

A receptive target indication

- Looking at the medical need of Indication A we can confirm that it exists.
- A scientific rational has also been confirmed by ISS and publications, showing Zepophan's efficacy in Indication A.
- The sub-population of Indication A has been described in ISSs but should be refined in further studies.

All parameters are met and a go-decision for Indication A would in this case be given.

Regulatory approval

The scientific support for Indication A is scarce, but with the size of the target population and its geographic distribution there are no clear signs of risking regulatory rejection.

Pricing approval

The same goes for the pricing approval, there are no clear signs of risking a pricing rejection.

As all primary parameters has been given a go-signal there is no reason of not looking into the business case for Indication A in the second step of the three-step repositioning model. Some indications may have

Table 7.1: Presentation of Indications A, B and C.

Competence area	Evaluation criteria	Indication A	Indication B	Indication C
Market	Patients US	2,900-14,500	57,000	8,000-48,000
Market	Patients EMENAR	4,500-22,500	n/a, 75,000 in Turkey	5,500–62,500
Market	Patients tot	7,400-37,000	7,500-60,000	13,500-110,500
Market	Treatment frequency	100 mg daily/9 month	100 mg daily/4 month	1-2 mg/kg and hour for 72 hours
Market	Syringes per year	2-10,1 M	0,9-7,3 M	0.67-1,1 M
Regulation	Medical need	Medium/High	High	High
Research	Mechanism evidence	Medium	High	Medium/High
Research	Optimal half-life	Long	Long	Short
Research	IV or SC	SC	SC	IV
Research	ISS or Publication	Yes	Yes	Yes
Research	Clinical program	Tapering/Safety	Tapering/Safety	Periodic/Safety
Research	Clinical program cost	205 MSEK	185 MSEK (potentially higher)	145 MSEK
Clinical program time	4.5-5 years	4.5-5 years	4.5-5 years	
Regulation	Orphan drug	Yes; USA/EU	Yes; USA/EU	Yes; USA/EU
Process	Geography	Normal distribution	Middle-East	Normal distribution
Market	Current competition	IVIGs	Interferon-alpha and SSRIs	Corticosteroids with csA
Market	Future competition	Depending on evidence	Rilonacept, Canacinumab	Rituximab
Process	Partnerhip	Cardiologists	Middle-East	-
Process	Treating physicians	Cardiologists/Rheumatologist	Rheumatologist	ICU/Rheumatologist
-	Key questions	Overlap with current indications	Prevalence Middle-East	Overlap with current indications

a weak scientific rational, or a fussy defined sub-population. In those cases it is up to the decision-maker to evaluate the probability of finding the rational or subpopulation. The decision to continue to the next step will further be a question of resources and how many options there are. Indication B would also pass the go/no-go decision with a warning at the pricing approval step. If the company would like to market the product in Turkey, where the prevalence of Indication B is high, they would risk a price cut. If only focusing on the U.S market the prospects are similar as to Indication A. As for Indication C the subpopulation is still not well defined and a no-go decision could be made at this stage. However, as only three indications are to be evaluated now, resource access will allow to continue with all three into the second step of the three-step repositioning model.

7.2 Evaluate secondary parameters

Now it is time to look at the secondary parameters. This is done through a scoring model where each parameter has to be evaluated on a scale from 0 to 5. As the risk of failure increases with a change of the product and a change of the product will require large investments on a product with already low margins late in its life cycle, a higher score will be given to indication options not needing changes. Hence, a low number will indicate that the need of doing a costly change in the product is high while a high number indicates that the need of that change is low. We start with the group of "total cost to launch". Each fulfillment score is multiplied with the weighing score and then summarized to get a total score of each indication.

Total cost to launch

- *Changes of IV/SC* - Zepophan can advantageously be continued as a subcutaneous syringe. Since no changes are needed the score becomes 2 (weight) x 5 (fulfillment) = 10.
- *Change in half-life* - Since Zepophan is given to patients with Indication A during a longer period of time it would be beneficial with a longer half-life. It is however not vital and the fulfillment will be given a 2, resulting in a total score of 2 x 2 = 4.
- *Change of dosage* - The dosage used in ISSs is the same dose as Zepophan is sold at today. Hence, no changes will be required. The score becomes: 4 x 5 = 20.
- *Change to periodic injections* - Indication A is not going to be given during short periods, giving the score of 4 x 5 = 20.
- *Size of patient group* - The patient group is very small and will fall under the category of being orphan which will give cost benefits.[1] The number of required studies may be fewer and so will the size of the studies, resulting in fewer costly patient visits. 4 x 4 = 16.
- *Number of treating physicians* - It is not completely understood by whom these patients will be treated, however, the size is probably not great and this parameter is given a fulfillment grade of two. 2 x 2 = 4.
- *Price of study-comparison-product* - The drug used today is fairly cheap and the cost will not be much bigger compared to a placebo or a "not-doing-anything" alternative. Further, there are no other known products in pipeline for The score becomes 5 x 5 = 25.
- *Treatment length* - Length of treatment and follow-up is neither long nor short and is therefor set to a 3. 4 x 3 = 12.
- *Specialist treatment centers* - Last parameter, these patients will probably not be treated at specialist centers. 1 x 3 = 3.

[1] To receive an orphan designation the prevalence of the disease has to be less than 1:1500 people in the United States and less than 1:2000 in the European Union, or if the population is larger the investments should not be likely to be covered by sales. In the European Union the drug also has to show significantly better effecacy than available options. An orphan designation would further give incentives such as tax . If market approved, the drug will get a market exclusivity for seven and ten years in the European Union and the United States respectivelly (FDA US Food and Drug Administration, n.d.; EMA European Medicines Agency, 2016).

This category gave a total score for Indication A at: 10 + 4 + 20 + 20 + 16 + 4 + 25 + 12 + 3 = 114. Indication B and C had scores of 97 and 120 respectively. The greatest drawback of indication B is the great risk of having to make comparison studies with a very expensive competitor that may file for that indication in the near future. As regards indication C a change of dosage may be necessary in order to make the treatment convenient and efficient for the patients. However, as these patients are treated at the intensive care untit, the saving of life is more important than a convienitent usage.

We may now continue with the same mindset to the group of "total income from sales".

Total income from sales

- *Size of patient group* - The size of the patient group is small. As a larger group is preferred when looking at a paying market it is given a 2 (a 1 can be given to a ultra orphan target population). The score becomes: 4 x 2 = 8.
- *Dosage per patient and year* - One syringe is given daily for approximately nine month which is a fairly large amount. 3 x 4 = 12.
- *Current competitor climate* - The current competitors for the subpopulation is a non-precision drug as well as a similar drug to Zepophan but with longer half-life. The latter has been Zepophan's main competitor during a long time and is distributed by one of Big Pharma. 4 x 4 = 16.
- *Future competitor climate* - In order to determine the future climate more has to be learned about the disease mechanism. As looking now the competition is not apparent. 5 x 3 = 15.
- *Expected price* - the only change that might be necessary for the drug to fit Indication A is a prolonged half-life, this is not likely to happen within the next coming years. Hence, we can assume the product to be the same and a great price increase is not likely to happen. The medical need is large and but a longer half-life would be to prefer. Further, the size of the population and the geographic distribution does not indicate a major reduction in price. In conclusion, the price can be expected to stay more or less the same. 5 x 3 = 15.
- *New patents* - A new patent for Zepophan for Indication A is far fetched, but not impossible through a longer half-life. 5 x 1 = 5.
- *Orphan designation* - Indication A does meet the requirements to obtain an orphan designation and will probably get one in the United States. 2 x 4 = 8.
- *USA market* - Indication A will most probably have a US market, even though it is estimated to be quite small (as can be seen in table 7.1). 5 x 4 = 20.
- *Required partnership* - As the patients of this disease will be treated by physicians not currently existing in Zepo's network a business partner could be useful in order to reach the target market. However, such relationship is not essential and it is possible for Zepo to perform the repositioning by themselves. 5 x 5 = 25.
- *Overlapping patient groups* - Indication A does have an overlap with another indication for Zepo which will decrease the amount of new potential patients. 4 x 3 = 12

The total score of the "total income from sale" category for Indication A is: 8 + 12 + 16 + 15 + 15 + 5 + 8 + 20 + 25 + 12 = 136. Indication B and C had scores of 124 and 164 respectively. What strengthens the case of Indication C its best chance of receiving a new price and patent due to changed dosage. Next category to evaluate is time to market.

Time to market

- *Orphan designation* - As been discussed earlier, Zepophan is likely to receive an orphan designation for Indication A and that will also shorten the time to market. 3 x 4 = 12.
- *Direct market access* - This is closely related to having a US market since they allow for a direct market access during price negotiations. 4 x 3 = 12
- *Supplementary data, ISS/publication* - There are some studies that may be used as supplementary data, however it is still quite scarce. 5 x 3 = 15.

- *Regional distribution* - Indication A can be assumed to be normally distributed. As an orphan indication it may therefor be hard to reach the target patients. 3 x 1 = 3.
- *Required follow-up time* - The length of the follow-up time is intermediate, around a year. 3 x 2 = 6
- *Relation to clinicians* - The treating physicians are not known by Zepo today. However, it is considered to be a reachable group. 2 x 2 = 4.
- *Relation to patients* - Zepo has today some relation to the patient group due to an overlap with another indication for Zepophan. 1 x 3 = 3.
- *Necessary product development* - Zepophan could be used in existing formulation in indication A, however, it by increasing its half-life it would be slightly more attractive to the market. 5 x 4 = 20

This final category gave a total score for Indication A of 12 + 12 + 15 + 3 + 6 + 4 + 3 + 20 = 75. Indication B and C had scores of 77 and 64 respectively.

The total score of Indication A within the second step of the three-step repositioning model is 325. Indication B and indication C had total scores of 298 and 348, respectively. Looking at all alternatives you will get a ranking with indications with most positive business case at a highest score. Depending on these ranking scores and the available resources the decision-maker will decide which indications to take into the last step of the three-step repositioning model. As regards to the three indications studied in this case-study, Indication C show to have the best economic prospect if a subpopulation is determined. Indication B should be left at this stage and Indiaction A and B can futher be evaluated in the third step of the three-step repositioning model.

7.3 Evaluate tertiary parameters

If the difference between the indications are small it is time to turn to the tertiary parameters, the business strategy. In this third step one should look at how well the indication fit the company strategy and if any synergies may be possible in order to facilitate market entrance for upcoming products in pipeline. As for Indication A it does fit the company vision of focusing on rare diseases. It is also a possible market for the next generation of Zepophan in pipeline, this may be both good and bad.

This description has hopefully given an idea of how to use the three-step repositioning model. The parameters, fulfillment grading, and weighting can preferably be refined and adjusted to the specific case.

Table 7.2: Ranking matrix of Indication A, B and C (I-A, I-B and I-C respectively) according to the fulfillment of secondary parameters.

Parameter	Weight	Fulfillment I-A	Fulfillment I-B	Fulfillment I-C
Total cost to launch				
Changes of IV/SC	2	5	5	2
Change in half-life	2	2	2	5
Change of dosage	4	5	5	4
Change to periodic injections	4	5	5	5
Size of patient group	4	4	4	4
Number of treating physicians	2	2	3	4
Price of study-comparison-product	5	5	2	5
Treatment length	4	3	3	5
Specialist treatment centers	1	3	3	5
Total income from sales				
Size of patient group	4	2	2	2
Dosage per patient and year	3	4	3	2
Current competitor climate	4	4	3	5
Future competitor climate	5	3	2	5
Expected price	5	3	3	4
New patents	5	1	1	3
Orphan designation	2	4	3	2
USA market	5	4	2	5
Required partnership	5	5	5	5
Overlapping patient groups	4	3	5	3
Time to market				
Orphan designation	3	4	3	2
Direct market access	4	3	3	5
Supplementary data, ISS/publication	5	3	3	1
Regional distribution	3	1	1	1
Required follow-up time	3	2	2	4
Relation to clinicians	2	2	4	3
Relation to patients	1	3	4	2
Necessary development	5	4	4	2
TOTAL SCORE		325	298	348

Chapter 8

Discussion

This chapter aims to discuss and evaluate the presented three-step repositioning model, created from empirics in this thesis. Its strengths and weaknesses will be discussed in relation to current literature, as well as from an ethical and sustainability perspective.

8.1 Coherence with literature

Six main categories were identified in this thesis: (1) medical need, (2) economic return, (3) scientific support, (4) timing, (5) life cycle extenders and (6) external relations. These categories with underlying factors were further analyzed and divided into three groups of parameters: primary, secondary and tertiary parameters, depending on their importance for the repositioning selection. By comparing these findings with the categories found in traditional R&D project selection, (1) strategic parameters, (2) technological parameters, (3) economical parameters, (4) market parameter, (5) other parameters, such as customer acceptance, timing, and risk, great similarities can be found. By having included all these perspectives in the three-step repositioning model I would argue that the model has captured the complexity of a repositioning initiative.

Strategic parameters

In the three-step repositioning model company strategy parameters were considered to be tertiary parameters as the repositioning was more about finding fast economic return for the company, than being coherent with company strategy. Other parameters that may be associated with "strategic parameters" are the topics within the category of external relations. These relations were discussed both in literature and during interviews. E.g. repositioning success factors identified in current literature included an engagement with regulatory authorities and payers early on in the process to decreases the risk of failure. This view was shared with the interviewees at Zepo.

One point where literature and interviewees had different views, was the question of strategic partnerships. In literature a business partnership was seen as a positive opportunity in order to spread the risk and gain necessary knowledge (Barratt and Frail, 2012; Novac, 2013). Among the interviewees this kind of partnership was not seen as positive, since the final return on investments would be decreased. Another interesting aspects regarding external relationships was the importance of caring for the regulatory relations. According to Rawlins (2004) the decisions are more commonly based on expert opinions rather than on hard facts, a statement that underlines the importance of good relationships with the regulatory authorities.

Further, what differs greatly compared to other industries is the weak focus on patient relations. Patients are the final consumer of the product, but the knowledge of their need is foremost collected through the relationships with the treating physicians. Some authors, (Kvesic, 2008; Cowlrick et al., 2011), claim that a closer relationship with patients will be necessary in order to optimize decision outcomes and succeed with LCM strategies. Being a company focusing on orphan markets, Zepo has a good chance of actually getting to know the patient population and this parameter should maybe have been valued as more important, than the responses in this study show.

Technological parameters

In terms of technological parameters the literature covered the aspect of the importance of the feasibility of using the drug in the intended indication. This was also targeted as a very important factor by the interviewees and was called "scientific support" in this thesis. The need of data to reduce cost and risk was also identified by literature and interviewees independently.

Further, the pricing and market access will greatly depend on the characteristics of the drug and certain changes might be necessary in order to attract the target market while a more extreme change in the product, such as a new dosage, would be needed in order to prevent substitute use of the old product.

Economical parameters

The economic return is a main focus in the three-step repositioning model. Parameters affecting the business-case are all gathered under the secondary parameters and is evaluated by an internal weighing.

According to Murteira et al. (2014*a*), the economic result of a repositioning will greatly depend on a change in administration route, by addressing an unmet need, and by keeping the brand name. This shows the interconnection between the parameters, as the unmet need would fit under the market parameters. The brand name can be considered a strategic parameter and change in administration route, fit as a technological parameter, while they all affect the economic parameters of the case.

Market parameters

Within the group of market parameters the medical need and life cycle extenders may be placed.

Looking at the results from interviews it is not very surprising that all interviewees valued the medical need high since the medical need in pharmaceutical industry equals to what is called a "market demand" in other industries. What differs with pharmaceutical industry however is the lack of a push possibility, why the existence of a market pull becomes more important. If there is no market demand there will be no business case.

Other parameters that may be placed in the group of market parameters are the market size and competitors. Current literature and the interviewees had the same view of the risk of increasing the market size without receiving any additional market exclusivities, which could expose the product to biosimilar production. As the chance is low for Zepo to receive a patent protecting the molecule it should be of interest to dodge the risk of being exposed to such competition and a smaller, low risk market may be the better choice.

A concern that was slightly touched upon in literature but that was stressed during interviews was the topic of pricing and payers. Barratt and Frail (2012) argued that a reimbursement by national health plans was essential for commercial success (hence placed under "market parameters"). Getting this reimbursement is once again connected to the medical need and medical impact of the drug compared to currently available treatments divided by the cost of the new drug. As Zepophan has a relatively low price compared to immediate competitors, such reimbursement should be possible if repositioning into markets with high medical need and where Zepophan shows great efficacy. The latter is often shown in orphan indications.

An important detail if seeking orphan designation is that such approval is dominated by drugs targeting patient groups of less than 10,000 individuals (Braun et al., 2010). This should be evaluated in relation to the fact that regulatory approval will benefit from a not too small target indication while the the pricing would benefit from a not too large indication.

Other parameters

Under this umbrella parameter customer acceptance, timing, and risks were mentioned in the R&D selection literature. As an equivalent to the customer acceptance, this thesis presents the medical need, as the need indicates a necessary market pull. Timing was considered a separate category in this thesis while risk was dispersed between the identified categories.

Risk factors that were determined by authors such as Barratt and Frail (2012) were foremost concerning the risk of failing existing markets due to an indication expansion. This risk was only touched upon by a few of the interviewees. However, such risk should be prioritized. If there is any risk of failing existing markets while not increasing the economic profitability, the repositioning initiative should be canceled from a business point of view. From an ethical perspective however, a cancellation is not as self-evident, as long as the medical impact increases with the expansion. It is also important that any

safety issues and unknown properties are revealed and not hidden by the company. However, non-relevant label warnings to the old indications will not benefit any part, not the company, nor the patients.

8.2 Company and societal impact

The importance of a repositioning model goes beyond the potential revenue for the company. It also has a social and sustainability impact that should be mentioned. Repositioning initiatives affect both company and society in short and long term. For example, there is a demand from stakeholders to not only prove medical benefits but also to bring real added value to society in order to obtain market access through regulatory and pricing approvals (Murteira et al., 2014*b*). Also, by directing the repositioning towards indications with high unmet medical needs the access to market will be faster and patients will receive possible life saving care while the company gets fast profit. Another benefit for the company if focusing on markets with unmet needs is the support from society that value such initiatives. This is a reason for orphan indications to be beneficial for repositioning initiatives (Drummond, 2008; Novac, 2013).

Finding multiple indications for a drug has been referred to as creating an "incremental blockbuster" (Barratt and Frail, 2012). Such process is also beneficial for both company and patients, as the company improves return on earlier investments while more patients in need of treatment will receive access to it. Repositioning gives a chance to companies to take their products from being orphan, defined by high risk and low revenue, to become a blockbuster, changing the equilibrium to become a low risk, high revenue product (Ashburn and Thor, 2004).

In order to further benefit the society the company ought to consider indications outside of the core-business to exploit the full potential of the product, which is valuable for both company and society. Any successful repositioning processes, providing patients with treatment to an acceptable cost is valuable to society. The more repositioning processes that receive regulatory and pricing approvals, the better for society. Less failures, more saved resources.

Timing of entering the market first or second was discussed by the interviewees. From a social health perspective it is more valuable to get drugs to new markets, however from a socio-economical perspective it is highly valuable to have competition in order to decrease product prices.

Further, the model presented in this thesis may have a positive economic impact if applied correctly to the case decision at hand. Evaluating the potential of several repositioning opportunities in a structured way should increase chances to succeed compared with a gut-feeling decision. It should reduce the risk of failure and increase the chance of economic return from the repositioning. However, this model has not been tested nor confirmed statistically and can therefor not guarantee any success.

8.3 Evaluation of the three-step repositioning model

To be successful in a repositioning process, according to Smith (2012), one has to consider both intellectual property and regulatory exclusivities since commercial success depend on these market exclusivities. This has been considered in the presented three-step repositioning model, as well as other success-factors mentioned in literature. However, I could not only consider what is said in literature since it generally focuses on conventional drugs, produced chemically in large quantities, and thus may differ in some aspects from parameters used in a biological drug repositioning for an orphan indication. Additional success-factors were therefore identified during the case study of Zepophan.

A repositioning process will involve several competences in a company, with focus on development, clinical studies, regulations, pricing, and commercial parameters. As the knowledge is scattered over several individuals it is valuable to collect and visualize this knowledge in one place. As a suggestion, in a selection-model, as done in this thesis. Such model will have its weaknesses as it may lack the ability to capture the complexity of the selection. A more thorough collaboration in a cross-functional team may be necessary in order to capture all parameters necessary to make an informed selection. The three-step repositioning model presented in this thesis should be tested for more cases and perhaps be complemented with additional parameters or different gradings in order to optimize the selection.

This three-step repositioning model was based on interviews with employees within the biopharmaceutical industry with focus on orphan drug development. I would therefor argue that it is within this niche the repositioning model primarily should be applicable. If used for repositioning through conventional drug development by pharmaceutical companies, minor changes may be necessary. Such changes should reflect the more immediate threats from generics compared to biosimilars, diverse regulatory preconditions, or even different company strategies that may exist in cases of conventional drug development.

Further, there are different sub-strategies within repositioning efforts (as can be seen in figure 2.6) and this thesis has followed one of these paths. This will limit the possibility to use the results presented for drugs following another path, such as before a market approval or after a patent expiry. It will however only necessitate minor changes in order to extrapolate to these branches of the classification tree. If the repositioning would be applied to a not already approved and marketed drug, as in the case of Zepophan, more data would be needed showing its safety profile. Larger data collections will, according to Dubey and Dubey (2009), increase the risk of failing the regulatory approval.

I would therefore further argue that the model may be used after minor changes to any repositioning following the same repositioning path as Zepophan in this case, orphan or not. If the repositioning on the other hand takes place before a market approval, changes to the model may be required in order to get a valuable selection of opportunities.

One can also consider to generalize the three-step repositioning model to other product development projects within other industries. In such case major changes should be made in order to fit the case and product. However, the main essence may be used. That is, having a strict go/no-go decision in order to fast eliminate alternatives deemed to fail and instead focus the resources to a limited amount of opportunities to evaluate their possibilities to succeed and bring economic value to the company. Moreover, how to value the connection to corporate strategy differs greatly between companies and industries and should in some cases be valued higher than in this case.

Chapter 9

Conclusion and future research

In this concluding chapter the final remarks are made. The chapter will summarize the main conclusions drawn from the conducted research in order to give concrete answers to the stated research questions. Further, to close this thesis, I will present my thoughts of future research that may be of interest to strengthen the academic knowledge of the phenomena of selecting repositioning opportunities.

9.1 Concluding words

The purpose of this master thesis was to explore the process of drug repositioning and to develop a repositioning model to be used for making smart repositioning choices. In order to achieve that purpose I have through a case study of a repositioning process provided answers to the research questions of this thesis: *What parameters are used as center of analysis for evaluating the potential of new indications in a repositioning strategy?* and *How should these parameters be weighted in relation to each other?* In summary, the concluding findings are as follows:

What parameters are used as center of analysis for evaluating the potential of new indications in a repositioning strategy?

This thesis argues that there are six main categories to consider before a repositioning. These are; (1) *medical need*, (2) *economic return*, (3) *scientific support*, (4) *timing*, (5) *life cycle extenders*, and (6) *external relations*. Within each category there is a number of detailed factors, presented in chapter 5. These categories were determined from empirics collected during interviews with experts within each field of research & development, clinical studies, regulation, pricing, and commercial. It is noteworthy to highlight that such diverse expertise gave a full perspective of the phenomena of repositioning. The identified factors also show to cover all categories mentioned in project selection literature to enable informed decisions, see table 2.1.

With these factors listed the second research question could be answered.

How should these parameters be weighted in relation to each other?

After having identified the parameters used for evaluating repositioning opportunities it was time to weight their mutual importance for the decision. This was made possible through answers from the interviews and the available literature on the topic of repositioning and R&D project selection. Three levels of parameters were identified, the primary, secondary, and tertiary parameters. The most important parameters, the primary parameters, consists of identified factors that are vital in order to take a drug through a repositioning to a new market. These are: (1) *a developed drug*, (2) *a receptive target market*, (3) *regulatory approval*, and (4) *pricing approval*. If any of the primary parameters are not fulfilled, the repositioning opportunity should be killed and resources should re-focus on remaining opportunities.

Within the secondary parameters you find: (1) *total cost to launch*, (2) *total income from sales*, and (3) *time to market*, all affecting the economic outcome of the repositioning (the business case). Each parameter has its sub-parameters that were given a weight depending on its importance for the decision. This weighing was inspired by both literature and interviews. By combining the two sources the model was strengthen and adjusted to a more general case. Further, each repositioning opportunity was evaluated through looking at how well it fulfills each sub-parameter and a total score was given to the

indication, reflecting on its economic prospect and probability of succeeding. By ranking the repositioning opportunities a smart choice is enabled.

In the third step of the three-way repositioning model the remaining opportunities can be evaluated based on its coherence with the overall company strategy by looking at: (1) *company mission*, (2) *pipeline strategies* and (3) *brand strategies*.

The answers to the research questions led to the fulfillment of the purpose of this thesis, to: *develop a repositioning model for selecting the most promising repositioning option*, presented in chapter 7. By combining previous literature of repositioning and R&D project selection and individual knowledge collected through interviews this thesis has contributed by filling a gap in the current repositioning literature. More specifically, by filling a gap of which parameters that should be considered, for enabling a successful repositioning and how these may be weighted in order to prioritize among different repositioning opportunities.

9.2 Areas of improvement and future research

All research has its limitations, and the study of this thesis is no exception. As Cowlrick et al. (2011) concluded in their paper, a study of a real case will offer valuable insights of how and why decisions are made. The result from such study may also allow for some generalization. However, one should keep in mind that personal interests and subjective views of the interviewees may bias the result. Hence, in order to allow for a trustworthy generalization, more confirming studies should be conducted as a complement to this single-case study.

Another aspect that may limit the use of this research are the many aspects of the phenomena, covering research and development to market strategy and strict regulations. As a single researcher with a limited amount of time for conducting the research, I might not have captured all aspects in a thorough way, resulting in a model not capturing the complexity of the reality. However, I would argue that a value of this model still exists. Having a model is always a start which allows for collecting and to sort otherwise dispersed knowledge. This model can further be built on and adjusted to fit a specific situation.

The topic of this thesis has been quite complex and challenging to grasp with its many perspectives and aspects. In order to confirm or refute the findings of this paper, and to strengthen the academic knowledge of the phenomena of repositioning and how to select among opportunities, I have some suggestions for future research:

- Each parameter could be analyzed separately in order to prove or disprove its accuracy. By studying the parameters in detail they may be refined to give a more reliable result for repositioning success. Such study may also reveal more important interconnections between the parameters that may influence the outcome.
- I further suggest making similar studies at other pharmaceutical companies. Such studies could confirm the generalization of the results found in this thesis while sophisticating the weighing of the parameters. It would further be valuable to statistically verify the presented model.
- To confirm the generalizability of these results at different levels it would further be interesting to look at repositioning of other candidates to compare e.g. biological and chemical drug repositioning, repositioning at other points in the development process or even repositioning in other industries.

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Appendices

Appendix A

Description of interviewees

This study has partly been based on interviews with employees at a middle sized pharmaceutical company, in this thesis referred to as Zepo. The interviewees come from five different fields within the company, namely: Research & Development, Clinical Studies, Regulatory, Pricing and Commercial. All interview subjects have experience of former and/or present repositioning initiatives as well as knowledge of Zepo and the three indications.

Interview 1: Principal Scientist

60 minutes long interview with focus on research & development, collaborations with academia and portfolio innovation. The Principal Scientist knew the product and the indications well after more than 15 years at Zepo.

Interview 2: Clinical Program Manager

50 minutes long interview with focus on clinical studies, life cycle management and post-market commitment. The Clinical Program Manager also assisted in filling out blanks in the technical and market analysis concerning clinical studies.

Interview 3: Global Director Health Outcomes

50 minutes long interview with focus on pricing strategies and pricing complications with Zepophan. The Global Director Health Outcomes had more than 20 years of experience as health-economist, knew Zepophan well and had superficial knowledge of the three indications.

Interview 4: Nordic Patient Access Lead

60 minutes long interview with focus on pricing in general cases of repositioning. The Nordic Patient Access Lead did was only familial with the indications but had experience from repositioning and pricing with other products.

Interview 5: Product Group Manager

80 minutes long interview with focus on commercial aspects of repositioning and Zepophan. The Product Group Manager was commercially responsible for Zepophan in the Nordic countries and had good knowledge of the three indications.

Interview 6: VP Global Brands

60 minutes long interview with focus on commercialization and repositioning strategies with a world wide perspective. With ten years at Zepo and commercial responsible for the global profitability the interviewee had good knowledge of product and indications.

Interview 7: Senior Director Biomedical Science

50 minutes long interview focusing on research & development, portfolio innovation and strategy Knew the product and indications, however not in detail.

Interview 8: Regulatory Affairs Manager I

60 minutes long interview with focus on regulatory affairs and manufacturing. Good knowledge of the product and superficial knowledge of the named indications.

Interview 9: Global Regulatory Affairs Manager

60 minutes long interview focusing on regulatory affairs and repositioning. The interviewee had experience of regulatory questions and was involved in the latest repositioning of Zepophan.

Interview 10: External Affairs & Patient Access

60 minutes long interview focusing on pricing during repositioning strategies with a world wide perspective. The interviewee had good knowledge of Zepophan and its possible indications.

Interview 11: Global HEOR & Country Patient Access Lead

60 minutes long interview with focus on pricing during repositioning strategies with a world wide perspective. The Global HEOR & Country Patient Access Lead had good knowledge of Zepophan and its possible indications.

Interview 12: Regulatory Affairs Manager II

75 minutes long interview with focus on regulatory aspects of repositioning. The interviewee had experience with the product and was involved in Zepo's last repositioning.

Interview 13: Clinical Program Leader

60 minutes long interview focusing on clinical studies. The Clinical Program Leader had experience of clinical studies and repositioning efforts. The interviewee had good knowledge of the drug and the three indications.

Appendix B

Interview template

The interview template presented below was used during all interviews. The open questions were focused on repositioning in order to provide answers to the first research question. These were followed by more specific questions adapted to each interviewee's competence area and the interview ended with asking the interviewees to grade a set of parameters. This list was extended during the interview period.

Interview questions

Each interview was initiated with a presentation of the research and the definition of "repositioning". Further, ethical and confidentiality concerns were discussed before starting the recorder.

1. Who are you? Please tell me about your background and current position.
2. What is your connection to Zepophan and Indication A, B, and C?
3. Have you participated in any repositioning projects?
4. What are the first thing you consider when standing with the task to evaluate different repositioning opportunities?
5. What else do you consider in your analysis?
6. What are the main pitfalls during a repositioning project?
7. What are the main differences between the three indications from a repositioning perspective?
8. *More specific questions concerning each interviewees competence area (Research & Development, Clinical Studies, Regulatory Affairs, Pricing, or Commercialization) to deepen knowledge and confirm answers.*

Grading-list

Please grade each factor according to its importance for a repositioning from 1-5 (1 – not important, 2 - neither important nor unimportant, 3 – quite important, 4 – important, 5 – very important)

Incidence

Prevalence

Patients US

Patients EMENAR

Patients tot

Treatment frequency

Syringes per year

Market segment

Current competition

Future competition

Mechanism evidence

Optimal half-life

IV or SC

Target product attribute

ISS or Publication

Completed clinical program

Clinical program cost

Research & Development time

Medical need

Orphan drug

Pricing

Geography

Collaboration with partner

Treating physicians

What should be added to the list?