EXPLORING THE VALLEY OF DEATH IN BIOPHARMA

A Master of Science Thesis

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VINTURA

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Master of Science Thesis

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A.C. Mannheimer

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Exploring the valley of death in Biopharma

by

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in partial fulfillment of the requirements for the degree of

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Executive summary

The pharmaceutical sector is more and more going in the direction of using living systems to produce the drugs, also known as biopharmaceuticals. The innovative capacity for biopharma firm has proven to be high, making them interesting sources for new innovative drugs for the market. Bringing a new medical drug to the market is a long and challenging process for companies. The average cost is about $1 billion with a time frame of 10 to 15 years from that an innovative idea is created until a drug is successfully launched in the market, and far from all ideas makes it all the way. This phase is also known as the 'Valley of Death', which only by the name indicates how difficult a trip across here is. However, many biopharma firms are still small in size compared with the huge pharma firms, and therefore have quite some troubles when traveling through the valley of death. In other words, they commonly lack key resources and capabilities to make it to the market.

The purpose of the thesis report is to explore the valley of death in the biopharmaceutical sector. The focus is to understand how biopharma firms experience the phase, and to identify key actors and factor that play a role here, and their interconnections to each other. Moreover, the aim is to identify various strategies that biopharma firms can use to overcome the barriers that stand in the way of successfully introducing an innovative product in the market. The main research question used was 'What are key actors, factors and strategies that impact how biopharma companies move a radically new product from invention to a first market introduction?'

In order to investigate this topic further, exploratory research was done to contribute to the current lack of understanding the valley of death in a comprehensive way. The research approach consisted of a combination of three different methods, to cover both theoretical and practical aspects on the topic. Additionally, the three methods were combined to tackle the exploratory research, since it wasn't known in advance where the most information would be found. The first method was systematic literature review, which studied the current literature stream from the search phrase 'valley of death' in the title of the articles. The second method was carrying out interviews within the organization of Vintura, a consultancy firm focusing on life sciences and health care topics. Finally, the third method was company interviews with four biopharma firms, by interviewing two persons within each firm. Each method was used

to answer all the sub questions in the thesis, and in the end all the results were consolidated into final answers to the sub questions, leading up to an answer for the main research question.

The literature review provided information from a historical and academic perspective, however the literature on the valley of death is quite limited. The Vintura interviews provided a practical approach for the topic, with more interconnections and strategies described. Finally, the company interviews with the biopharma firms gave insights straight from the firms themselves, on how they experience the innovation process and its challenges. The interview set-up for the biopharma company interviews was interactive, resulting in interesting visual overviews of interconnections between actors and factors. The combination of all results provided good answers to the sub questions, and in total to the main research question.

The valley of death is an uncertain and risky phase for companies that takes between 10 to 15 years to complete. Overall, the results show that biopharma firms should aim to achieve six goals in the valley of death: (1) develop the right product, (2) find sufficient funding, (3) have the right skills & resources at the right time, (4) make an intellectual property set-up, (5) plan & execute clinical trials, and (6) increase product development speed. In other words, aiming to reach these goals in the best way would provide a higher chance to deal with the valley of death successfully. Moreover, many key actors and factors were found. Examples of actors are regulatory authorities, contract organizations, hospitals, and various scientists, while some examples of factors are design of clinical trials, access to capital, and human resources. The thesis results also provided many relations and interconnections between actors and factors, connected to the six main goals presented. As an example, in order to work towards the goal to develop the right product, the actor 'project manager' in combination with the factor 'leadership skills' showed to be a critical element needed to get a good process running. Similar interconnections were found for other actors and factor per main goal. Finally, many strategy suggestions were identified from all the research methods, with specific links between a strategy and a barrier. An example of a strategy is 'evaluate knowledge gained in clinical trials and tackle issues', when dealing with commercial issues with the product.

From all the results in the thesis, a theoretical model was created to visualize causal relationships between actors, factors and strategies in the valley of death. The model shows an overview of the six goals, with a detailed sub model per goal explaining the dynamics and connections. The model consists of the following elements: (1) a goal, which is one of the six main goals, (2) facilitators, which are actors or factors that positively contribute to reach the goal, (3) barriers, which are actors or factors that are blocking the goal, and (4) strategies, which are specific suggestions on how to tackle each barrier. Overall, this model provides a visual and practically usable tool to understand the main mechanisms in the valley of death, and concrete suggestions on how to increase the chances to survive the valley of death. The model can have a managerial impact for biopharma firms, by offering an overview of the key goals and the challenges. Furthermore, the model adds to the literature and previous research by providing an overview of interconnections and strategies that previously could not be found in the literature.

It is recommended to verify the model through further research, by qualitative or quantitative approaches to find out if companies in the biopharma sector agree with it. Moreover, the model could partly be valid for the pharmaceutical industry, or be adapted to other relevant high-tech industries, which can then be investigated in future research.

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Abbreviations

CA	Competent Authorities
CEC	Central Ethics Committee
CEO	Chief Executive Officer
CMO	Contract Manufacturing Organization
CRO	Contract Research Organization
EMA	European Medicines Agency
FDA	Food and Drug Administration
HTA	Health Technology Assessment
HTS	High-Throughput Screening
IP	Intellectual Property
IT	Information Technology
KOL	Key Opinion Leader
NCE	New Chemical Entities
NPD	New Product Development
$R\&D$	Research and Development
SQ	Sub Question

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Chapter 1

Introduction

The introduction chapter will introduce the thesis through eight different subsections. First, the problem will be introduced, including a short industry description, innovation model, and definitions of the valley of death. Second, the problem statement is presented, following from the problem introduction. Following this, the problem owners TU Delft and Vintura are presented, and in the next section the objectives with this thesis project. The fifth section is about the scientific and societal relevance, where the thesis contributions are described and how they benefit the knowledge increase in science and for the society. After this, the research questions are presented, consisting of one main question and four sub questions. Following this is a section describing the research approach, presenting the three different approaches: systematic literature review, Vintura interviews, and company interviews with biopharmaceutical firms. The final section presents the structure of the rest of the report.

1-1 Problem Introduction

In this section, the problem for the thesis is introduced more in detail, with the goal of presenting the industry context, the innovation theory used, and the definition of the valley of death.

1-1-1 Biopharma industry - a new twist on the pharmaceutical industry

Traditional pharmaceutical industry

The pharmaceutical industry has been thriving thanks to sales revenue on so-called blockbuster drugs, that target large market segments (Rai, Reichman et al. 2008) and generates sales of more than $1 billion (Carroll 2009). However, the once prosperous and profitable pharmaceutical industry has lately experienced a downscaling and the companies have struggled to launch new products in the market to solve the increasing need for health solutions

in the society (Clark 2013). Today's globalized business climate includes many actors, making it crucial to keep innovating to stay competitive and survive in the market. During the past decades, government funding for the pharmaceutical industry has seen a 10-fold increase (Coller and Califf 2009), while the number of new drugs introduced in the market unexpectedly is decreasing. Pharmaceutical firms have struggled to create essentially new small molecule drugs working on new targets, and at the same time their blockbuster patents are expiring (Rai, Reichman et al. 2008).

Innovative biopharma firms

Over the last decades, the traditional pharma firms have experienced a change in the industry since many small biotechnology firms have been developed and established themselves in the market (Gans and Stern 2004). A biotech firm is typically a research-intensive, small company, often generated as a spinoff or startup from a prominent research university (Khilji, Mroczkowski et al. 2006). Biotechnology is an engineering discipline that applies the knowledge of biology into developing products for a final market. If a biotech firm produces pharmaceutical products, called biopharmaceuticals, it does so through the use of living systems, such as yeast cells, bacteria or mammalian cells. This is opposed to traditional pharmaceuticals, which are produced using plant-based compounds or chemical synthesis (MorganMcKinley 2013). The development of using biotechnology to make pharmaceutical products have led to a change in Research and Development (R&D) structure in many traditional pharma firms. It has become common for pharma firms to acquire a research-intensive biotech firm and integrate that technology into their business practices. This also benefits the smaller biotech firms, since they then can gain access to the experience and infrastructure of the larger pharma firm (Gans and Stern 2003). However, getting acquired also means that the biopharma firm loses some control over decisions and operations, which can be a downside.

The biotech firms that produce biopharmaceuticals are also called biopharma firms. In figure 1-1, the main differences between biopharma and pharma regarding production method and market structure is illustrated. Compared with traditional large pharma firms, the biopharma firms vary more in size and can have very different product portfolio strategies. Some biopharma firms are well-established and have several drugs in the market, while others are early-stage firms with only one or two products in the pipeline (Guedj and Scharfstein 2004). Examples of biopharmaceutical products are proteins such as enzymes and antibodies, all produced or engineered to target a certain disease. These are sensitive products since they are produced in living systems, meaning they need to be handled and transported in a different way than classic pharmaceutical products.

Product development process

The new product development process in a biopharma firm is in general time-consuming, risky and resource-intensive (Xia and Roper 2008), with an average cost of $1 billion to get a drug to the market (Hudson and Khazragui 2013). There are six standard steps that both biopharma and pharma firms take when developing a new drug (Sabatier, Mangematin et al. 2010): (1) Focus & target identification, (2) Discovery & R&D, (3) Pre-clinical testing, (4) Clinical trials, (5) Launch preparation, and (6) Commercial activities. Figure 1-2 shows an overview of these six phases in chronological order.

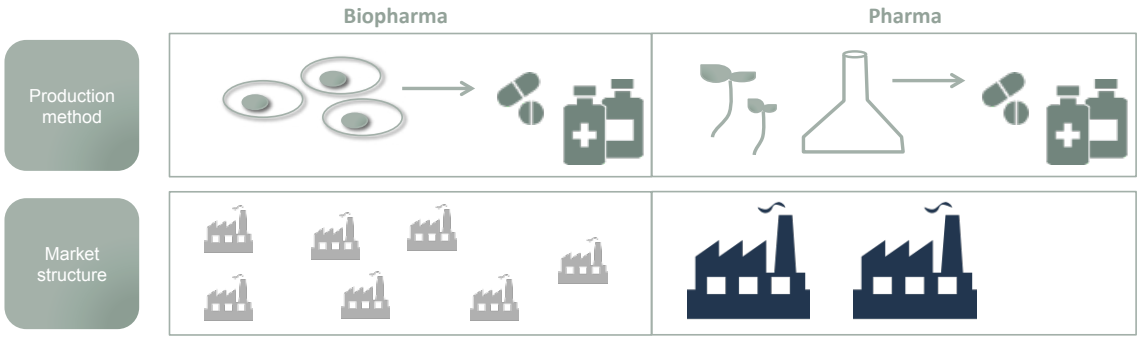

Figure 1-1: Differences in production method and market structure between biopharma and pharma firms

Figure 1-2: Standard steps in drug development for biopharma and pharma firms

In order to get an idea all the way through to a commercial product, a lot of different resources and capabilities are needed. In general, biopharma firms are good at carrying out the activities in the first two steps due to their innovative capacity. This is a risky time period with uncertainty about the results, and the activities are usually funded by venture capitalists (Sabatier, Mangematin et al. 2010). When entering the pre-clinical testing and clinical trials phases, the amount of capital and other resources needed increase significantly (Guedj and Scharfstein 2004). In the pre-clinical phase a first batch of the drug is manufactured and then tested on animals, before starting the clinical phase where the drug is tested on humans. It is common that the biopharma firm seeks partners to get support with pre-clinical and clinical activities, but the partners want to see promising results in order to make the investment (Sabatier, Mangematin et al. 2010). Another possibility is that a larger firm acquires the biopharma firm completely during the early clinical phase, and carries out the remaining activities to launch the final product.

Regulatory environment

The biopharma sector is very strictly regulated, comparable with the pharma sector, since the products are interacting with the human body. Regulatory bodies such as governments, Food and Drug Administration (FDA) in the U.S. and European Medicines Agency (EMA) in Europe have a large influence on what products that will be registered in the market. The so-called Health Technology Assessment (HTA) agencies are also involved in the market access process, providing criteria that the firms have to meet in order to launch their products. This means that the biopharma firms need competence in the regulatory area to know what the criteria and rules they need to follow for their specific product to be approved in the market.

1-1-2 Evolutionary innovation model

In order to understand how an invention gets turned into a marketed innovative product, an evolutionary model is used, presented in figure 1-3. This model is developed by Ortt and Schoormans (2004) and shows the pattern of development and diffusion of radically new products in the market. This framework consists of three defined phases: (1) Innovation phase, (2) Market adaptation phase, and (3) Market stabilization phase. Before the innovation phase is happening, there are pre-invention activities taking place.

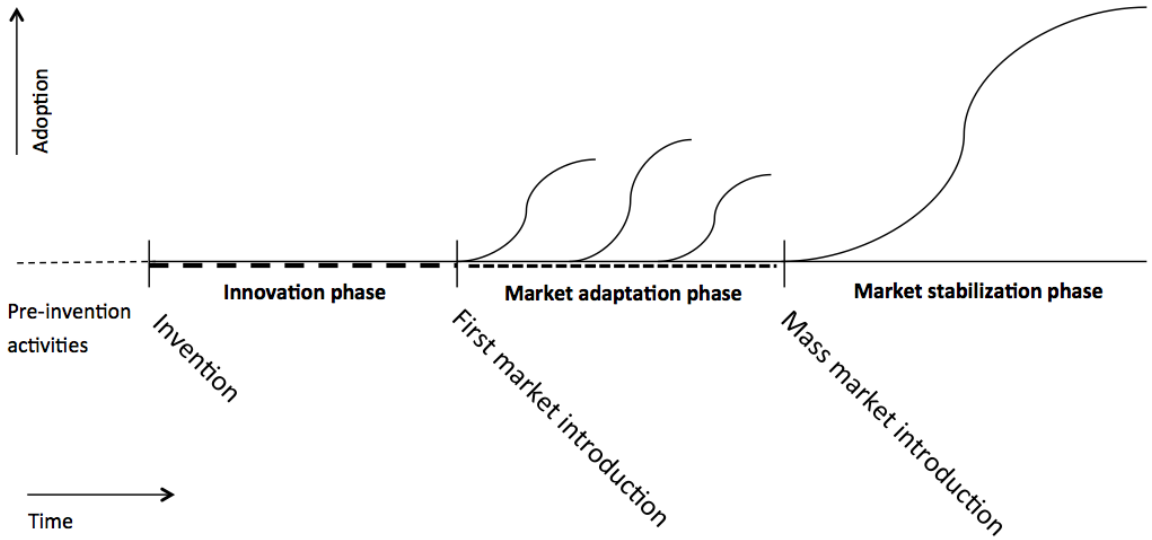

Figure 1-3: Pattern of diffusion and development (Ortt and Schoormans 2004)

This model has been built on more than 100 different cases with radically new products from various industries. The order, length, and existence of the phases can therefore be adapted to fit to a certain industry, making it a flexible theoretical model. This thesis research is focusing on exploring the first phase in this model: the innovation phase. The innovation phase is where an invented technology gets transformed into a product that can be introduced in the market. The estimation of the length of this phase has varied considerably from previous research, from everything between 10 up until 28 years, with examples from various industries (Ortt

and Schoormans 2004). At this point, there are still many uncertainties about the innovation phase, regarding its actors, factors, mechanisms and suitable strategies to get through the phase.

1-1-3 Valley of Death - the phase between invention and first market introduction

The process of bringing a radically new product to the market includes many steps and requires the right resources for a company. During this phase, between invention and first market introduction, many factors can influence the company performance. This phase is also known as the "Valley of Death", since many technologies fail to reach the market here. According to Markham, Ward et al. (2010), the valley of death is the phase between research and New Product Development (NPD), where the whole impact of organizational environment is taken into account. According to Roberts, Fischhoff et al. (2012), valley of death is the phase: *"where promising scientific discoveries linger and die."* Other authors describe the valley of death as the situation when a technology does not succeed in reaching the market because of not being able to move from the demonstration phase to the commercialization phase (Frank, Sink et al. 1996).

The valley of death is a phase that is present in many technological fields where breakthrough innovations are developed. The pharmaceutical industry is an example where traversing the valley of death means bridging the gap between basic research and clinical applications. In other words, performing so called translational research (Butler 2008), where the basic research discoveries become turned into products that will improve the life of patients. In translational medicine, the patient's health is the focus of the final outcome of the research (Wong 2014), meaning that the clinical application area is shaping the basic research needed to reach that goal. However, there is still a lot of basic research that is performed without an end product in mind, resulting in a lot of unused basic research findings. According to Rai, Reichman et al. (2008), the valley of death in pharma separates upstream research on biological macromolecules, such as genes and proteins, from downstream drug candidates.

Thus, within the literature that covers the pharmaceutical industry, it is spoken of a definition of the valley of death that refers to the valley that exists between basic and the clinical research activities. In figure 1-4 this is marked as "Literature Valley of Death". However, this definition neglects the challenges in the clinical research, which are key in the drug development, and instead includes basic research activities performed before the point of invention. In other words, the literature focuses on the translation from basic research into clinical practice, but does not include the activities closer to commercialization.

In the context of this thesis, the valley of death is therefore defined to be the first phase in Ortt and Schoorman's model, the so-called innovation phase. In other words, this is the phase between invention and a first market introduction of a radically new product. This is illustrated with the green arrow in figure 1-4, which shows a zoomed-in version of that phase from the Ortt model.

The current research about the valley of death mostly focuses on the financial perspective, however there are several other perspectives to investigate to be able to understand the mechanisms in the valley of death. The scope of this thesis will therefore cover the whole

range between invention until a first market introduction, to present all the actors, factors and strategies, with a focus on biopharmaceutical firms.

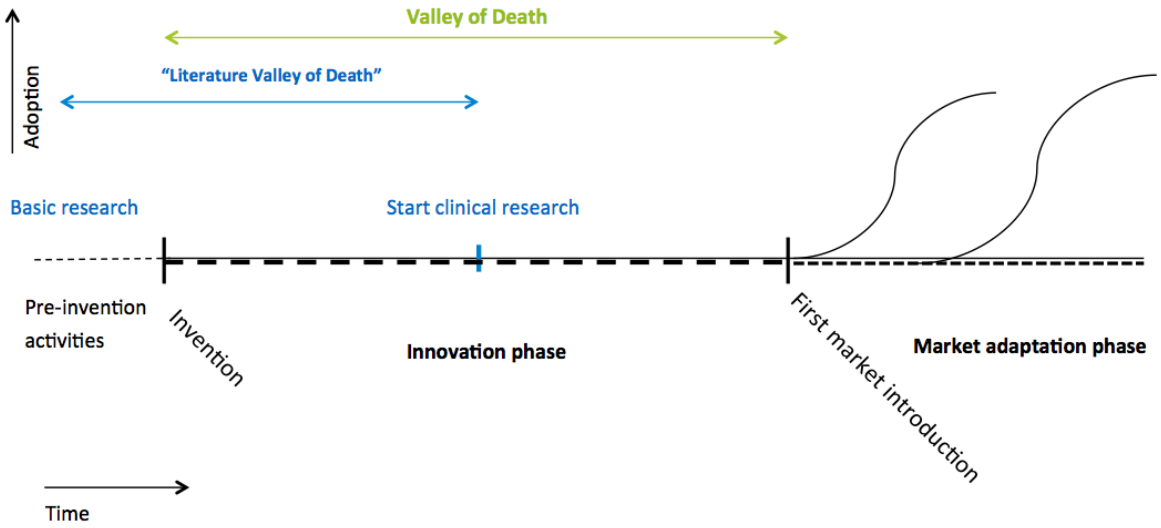

Figure 1-4: Definition of valley of death in this thesis, and illustration of the literature valley of death

This definition of the valley of death can be specified one level deeper, by showing how the different steps in the pharma and biopharma product development process fits in the valley of death. In figure 1-5, it can be seen that the four middle steps in this process fits into the time frame of the valley of death. These steps all require a lot of resources, human, financial and technological, showing once again that the whole phase is very resource-intensive.

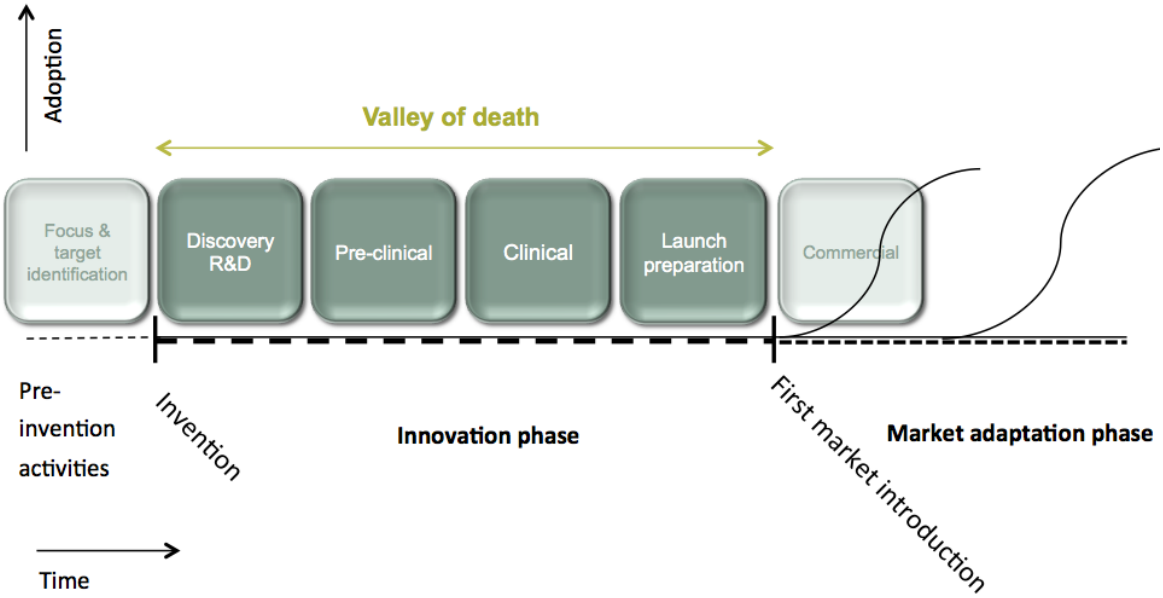

Figure 1-5: Drug development steps in the valley of death

When a new drug is under development there are many uncertainties, especially regarding the safety, efficacy and total performance of the final product. This influences investors and other partners to be reluctant to invest and collaborate, because the product development process is risky, uncertain and very expensive. As mentioned earlier, the phase is very resource-intensive, thus a lack of investors and partners further enhances the existence of a valley of death. The strict regulations also means that the biopharma firms need to go through a complex and time-consuming process of registering the drug in the market, contributing further to causing a valley of death, since it will take even longer before the product is launched in the market and can generate revenue streams.

1-2 Problem statement

The phenomenon of the valley of death-phase is well-known in many industries where radically new technologies are developed, however there is limited understanding in what the key factors and strategies are in this phase, influencing how firms move a radically new product from invention to a first market introduction. It is known that the finances play a major role during this phase, since the development and commercialization of a new product is a costly process (Hudson and Khazragui (2013), Roberts, Fischhoff et al. (2012)), however what other factors play a role is uncertain, especially regarding their interconnections.

As mentioned earlier, in the past decades the investment in new drug development has drastically increased, with the intention to cover the growing need for health solutions in the society (Clark 2013). At the same time, unexpectedly, the number of new drugs approved in the market has decreased (Rai, Reichman et al. 2008). This suggests that the pharmaceutical industry is struggling with crossing the valley of death, defined by Clark (2013) as *"a wasteland of exceptionally poor productivity where potentially exciting research discoveries funded largely by taxpayers fall off the precipice on one side of the valet, fail to traverse the development terrain in the valley, and fail to make the onward journey to benefit patients"*. There is therefore a societal urgency to understand the valley of death in the pharmaceutical sector, and with the recent addition of biotechnology, a focus on biopharmaceutical firms could generate interesting insights that includes the transition from traditional pharma to the fusion of these two industries as biopharma.

1-3 Problem owner

There are several problem owners within the scope of this thesis. The Master's thesis research will be done as collaboration between TU Delft and Vintura, a consultancy firm specialized in the healthcare and life sciences sector. The company was founded in year 2000 and employs around 25 experiences professionals. Vintura is a suitable partner due to their industry experience and network of clients in the (bio) pharmaceutical industry. During the project, Vintura will serve as a kind of "hub" for reaching out to suitable biopharmaceutical firms for pursuing the company interviews. Currently Vintura is aiming to expand their knowledge about the biotechnology sector and the use of biotechnology in the pharmaceutical industry, which is another reason for their participation in the project. Vintura is a problem owner in this thesis since the outcome of the study will be translated as far as possible to the business

setting of Vintura. Through this, Vintura can apply the findings in their advisory services towards clients in the health care sector.

Other than Vintura, the pharma/biopharma sector itself also is a problem owner. The primary findings will be derived from the company and managerial perspective, and the results can directly contribute to an increased understanding of this industry.

Finally, this thesis research will add to/expand the model of Ortt and Schoormans (2004), by pursuing exploratory research on the first phase in the model. Up until this point, the research focus has been on the market adaptation phase and understanding how companies use niche strategies to get through here. Two previous Master's thesis projects have focused on this market adaptation phase of the model by Ortt and Schoormans (2004). One project is focused on creating a dynamic framework for the selection of niche strategies when introducing a new product (Bruinsma 2015). The second project is about sequences of niche strategies in the automotive sector, investigated through multiple case studies (Vintila 2015). In one article by Ortt, Kamp and Doe, the case of kite-based airborne wind energy has been studied regarding what niche strategy selection is suitable to introduce this technology system in the market. This model is identifying market situations with certain barriers, and couples this to the choice of a certain niche strategy. The outcomes of the research will be discussed and compared with the niche strategy model in chapter 7. The research in this thesis aims to develop a theoretical model that can be applied in the innovation phase of the model by Ortt and Schoormans (2004).

1-4 Objectives

The objectives for this thesis research are:

- To understand the phase known as the valley of death, and which actors and factors are involved there
- To understand how these actors and factors are interconnected within this phase
- To define and/or develop strategies for companies, that are commercializing radically new innovations, to deal with this phase
- To contribute to the understanding of the biopharmaceutical industry regarding the valley of death
- To contribute with knowledge that can be used within the business of Vintura

1-5 Scientific and Societal Relevance

From a scientific perspective, this Master's thesis will make an academic contribution by providing additional understanding of the first phase in the framework developed by Ortt and Schoormans (2004). Furthermore, the thesis can result in the creation of a theoretical model showing interconnections and mechanisms in the valley of death. The current literature is limited in understanding the valley of death and the actors and factors involved here. This

thesis aims to identify these and to add knowledge about how they interconnect with each other, and strategies for companies to get through the valley of death.

Understanding the valley of death is also relevant from a societal perspective. On one hand, it lies within the interest of the society to grasp the challenges within the valley of death, since a lot of tax money is used to fund research and development. In order to bring the full potential of health innovations to patients, these challenges need to be understood and overcome. With an aging population is becomes critical to bring innovative medicines to the market to solve diseases such as Alzheimer's and cancer. On the other hand, it is also relevant for the industry actors and the field, i.e. the companies, to gain a better understanding of the valley of death. This could create more awareness in the industry towards these factors, and how to tackle the challenges. More specifically, the findings will have a managerial impact since managers in the biopharma firms that are experiencing the valley of death can use them to plan and deal with the challenges.

Moreover, the findings of this Master's thesis can be applied in the business setting of the consultancy firm Vintura, to contribute to solving problems in the health sector. It is relevant for Vintura to further understand how the companies in the field of pharma and biopharma experience the valley of death and what the main challenges are. By doing so, Vintura can potentially improve the business of those companies through providing advisory services towards their clients.

1-6 Research questions

Based on the problem description and the research objectives, the thesis will investigate the following main research question:

"What are key actors, factors and strategies that impact how biopharma companies move a radically new product from invention to a first market introduction?"

To answer this question, the following sub questions (SQ) have been defined:

SQ1: *How does the phase between invention to a first market introduction look like for biopharma companies?*

SQ2: *What are the key actors and factors in this phase that affects the performance of the biopharma companies?*

SQ3: *How are the actors and factors in this phase interconnected?*

SQ4: *What are strategies for biopharma companies to deal with this phase?*

1-7 Research approach

In order to add more expertise and experience from the (bio) pharmaceutical industry, this Master's thesis will be performed as collaboration with the Dutch consultancy firm Vintura, as explained in section 1-3.

In order to carry out the proposed research, the following research methodology is going to be used to find an answer to the main question and the sub questions. The research will

consist of three main parts; (1) a systematic literature review, (2) semi-structured interviews with employees from Vintura, and (3) company interviews with biopharmaceutical companies (see figure 1-6 for a visual overview). The first two parts will cover the existing knowledge about the topic, by looking at the literature and the knowledge in Vintura. The third part, company interviews, will add a deeper understanding and bring new knowledge to the table.

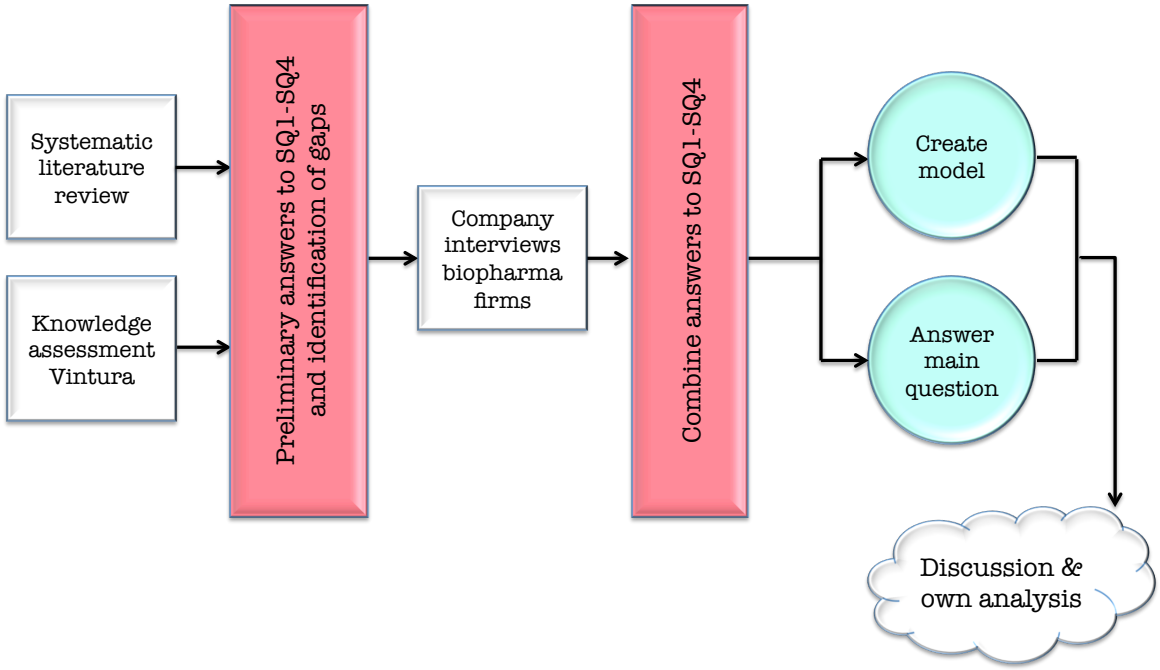

Figure 1-6: Research design for thesis

Initially, a thorough systematic literature review will be carried out to define what is already known in the area of valley of death. The search phrase that is used is "Valley of Death" within quotation marks. This returns around 150 hits in Google Scholar when it is searched within the title of the article. From this, a selection was made based on defined criteria. Criteria for inclusion are if the article has either: a company perspective, pharma/biotech perspective, describing the valley of death, or has an innovation/management/strategy perspective. Criteria for exclusion are if the article has either: a financial/economical perspective, a policy perspective, an educational perspective, a psychological/philosophical perspective, or a too technical perspective.

The second main part of the thesis is semi-structured interviews with Vintura, assessing their knowledge in the topic of the Valley of Death. This is done by one-to-one interviews, structured according to the research questions, but with an open approach to let the interviewee tell what comes to her or his mind. Through Vintura's experience in the field of pharma and health care, they provide a more practical perspective on the research questions, in comparison with the theoretical perspective in the literature. Five interviews have been performed to cover the Vintura knowledge level within the pharma/biotech and healthcare sector. One of the interviewees is from the external network of Vintura.

The findings from part one and two will be added together, to already compare the information and point out the gaps that are still remaining. The reason for this is to already assess the

findings to be able to get the most out of the company interviews studies as possible.

Finally, the third main part of the thesis consists of company interviews in the field of biopharma. This part was done to gain in-depth knowledge about how the biopharmaceutical companies themselves see this development phase, and how they deal with it. The company interviews have been done through interactive interviews, using the research questions as a red thread through the discussion. The selection of appropriate companies was done together with Vintura.

After this, a theoretical model has been created from all the results, and the main research question could be answered. From these parts there was also a discussion and analysis from the author, reflecting on the research findings and their implications and limitations.

1-8 Structure of the Report

The rest of this thesis is structured as follows: chapter 2 is about the systematic literature review, describing the methodology and the results per sub question. In chapter 3 the semi-structured interviews within Vintura are presented, with both methodology and the results from the interviews, the later are split per sub question. Chapter 4 contains the conclusions drawn from adding the findings from the literature together with the results from the interviews in Vintura. Through this, focus points for the upcoming company interviews will be presented. Following this is chapter 5, which is about the company interviews regarding methodology, description of each company, and results from the interviews within each company. The chapter ends with a short analysis where the various company interview results will be compared. In chapter 6 there is a comparison of all results, and the research questions will be answered, followed by the presentation of the model created from the results. Finally, chapter 7 includes further conclusion and discussion towards future research in this area.

Chapter 2

Systematic literature review

This systematic literature review is the first out of three main research components in this Master's thesis. Identifying and analyzing the selected literature gives a good understanding about the topic and provides a knowledge base for further developing the research and see where the knowledge gaps are. Pursuing it in a systematic way also enhances the quality of the review since its structure allows for a clearer and more reliable overview of the current knowledge. In this chapter the systematic literature review is described in more detail. First, an introduction about the literature review is made, describing how it fits into the rest of the research. Following this, the methodology used for the review is explained, and finally the results with regard to the specific sub questions are presented.

2-1 Methodology

The chosen methodology for this literature review is a systematic literature review. A systematic review means that the literature search is done in a structured way, such that it can be replicable and has a transparent approach (Denyer and Tranfield 2009). All the information is structured in a matrix, which makes the analysis clearer and much more efficient. Pursuing a systematic review also reduces the bias of the author, since all the decisions taken are justified by explanation (Denyer and Tranfield 2009). The first step for the review was to select a suitable search phrase to use in Google Scholar, in order to make a search that generated an appropriate number of articles to analyze. In other words, the scope of the article search has to be narrowed down to such an extent that it is possible to use as a base for a thesis. Using a search phrase that generated around 150 hits[1] in Google Scholar defined the size of the scope of articles. After trying out different alternatives, the phrase "Valley of Death" within quotation marks generated 141 hits when searched for in the article title, and with exclusion of patents and citations. This was decided to be a suitable set of literature, due to its size and its connection to the desired thesis topic.

[1] Rule of thumb for a suitable scope size

The following step was to sort the set of 141 publications and select which publications to use further and to study in-depth. Selections were made by deciding on selection criteria for inclusion or exclusion, and then apply these criteria to each and every one of the 141 publications. The criteria are presented in table 2-1. It should be emphasized that for a publication to be selected/not selected, it was sufficient to fulfill at least one of the criteria for either inclusion or exclusion.

Table 2-1: Selection criteria for inclusion or exclusion of publications

Criteria for inclusion	Criteria for exclusion
Company perspective	Policy perspective
Pharma/Biopharma relation	Financial/Economical perspective
Innovation perspective	Teaching perspective
Management/Strategy perspective	Psychological/Philosophical perspective
Describing the valley of death	Too technical perspective

Criteria for inclusion

The reason that the first inclusion criterion is "company perspective" is because of the limited time frame for the thesis project, and therefore the choice to focus the work from that perspective. The second criterion, "pharma/biopharma relation" is an inclusion criterion since that is the industry that is the focus in this thesis. Moreover, the majority of the literature about valley of death is in the field of pharma/biopharma already, which makes it a suitable industry choice. The third and the fourth criteria, "innovation perspective" and "management/strategy perspective" are chosen since this is the approach that will be used in the thesis. The framework by Ortt and Schoormans (2004) that is used as a base is also within the field of innovation management, which is why these criteria for inclusion are used. Finally the fifth inclusion criterion, "describing the valley of death", is used since the nature of this research is exploratory. Therefore it is valuable to find articles that describe how the valley of death looks like and what the mechanisms in that phase are.

Criteria for exclusion

The first and second criteria for exclusion are "policy perspective" and "financial/economical perspective", due to the previous explanation that the focus will be on the company perspective in this thesis. The third criterion, "teaching perspective" is used since there are some articles focusing on the teaching perspective for including studying the valley of death in university courses, which is not relevant for the thesis. The fourth criterion, "psychological/philosophical perspective" is also applied as an exclusion criterion since it is focused on an individual perspective, which is not included in the focus area. The final exclusion criterion is "too technical perspective", referring to the articles that are focusing on the technical details of an innovation. This is not included, since the thesis is focusing on understanding the valley of death on a higher level. Most of these articles were from other industries than pharma/biopharma, e.g. aerospace and environmental technologies, meaning they could have provided a different perspective. However, due to the focused technical perspective that they

had, it was chosen to not include them, since it was hard to apply to the pharma/biopharma sector.

The third step was then to create a matrix to use as a place to sort and structure the information that would be extracted from the publications. The columns contained titles about general information for the publication, together with the four sub questions. Each publication was read and analyzed to be able to extract the relevant information and place it into the matrix columns. All of the publications generated some information about the topic of valley of death that was summarized in the matrix.

By using this systematic way of extracting information, many publications could be studied in a thorough and structured manner.

2-2 Results

In this section the results from the systematic literature review are presented. The majority of the articles are focused on the pharmaceutical industry, but since there are similarities in how a biopharma firm brings a product to the market, the findings from the literature can still be applied in the biopharma field as well. However, it should be emphasized that much of the literature uses the definition of valley of death presented in figure 1-4 as "literature valley of death". This means that the literature includes some activities from before the point of invention, which actually lies outside the scope of the thesis. When this is the case it will be further explained. The subsections below present the results that were found per research question. For some questions there were more results, such as the descriptive questions, and in other cases it can be seen that the literature review must be complemented with other research methods to be able to answer the questions.

2-2-1 Results SQ1

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

The first sub question is dealing with the investigation of how the phase between invention and a first market introduction, the valley of death, looks like for biopharma companies. For this sub question, the literature review returned some useful findings regarding different definitions and time span of valley of death, and about some main activities that take place in this phase for the companies.

Different definitions of the Valley of Death

The valley of death has been described as the situation where a technology is failing to reach the market since it is not able to move from the demonstration phase towards the commercialization phase (Frank, Sink et al. 1996). According to Roberts, Fischhoff et al. (2012), valley of death is the phase: *"where promising scientific discoveries linger and die"*, as also mentioned in subsection 1-1-3. In other words, the technology does not cross the chasm that lies between the proof-of-concept and its use to benefit customers (Beach 2013). The

initially exciting breakthroughs made by scientists get published and receive a lot of attention, although several years later they fail to be translated into products that can benefit the society (Wong 2014). There are relative more resources in the shape of research expertise on one side of the valley, and more resources on the other side in the shape of commercialization knowledge. Thus, the valley of death is the corridor between research and New Product Development, which is a path critical to pass through to be able to commercialize a technology (Markham (2004), (Markham, Ward et al. 2010). During the valley of death, three roles are important in the role-theory of innovation: champion, sponsor and gatekeeper, where the champion adopts and advocates the project, the sponsor provides the necessary resources, and the gatekeeper makes the decisions about what projects to take further (Markham, Ward et al. 2010). According to Clark (2013), the valley of death is actually much larger than it is often described. It does not only cover one valley, but is made up of several valleys, representing different challenges for specific time periods in the process of taking a new product to the market. Moreover, Clark (2013) emphasizes that there are more reasons than only financial shortage that gives rise to a valley of death, it's rather the result of a complex system failure that requires a system approach to be dealt with.

The term valley of death is frequently used in the pharmaceutical industry to describe the challenging phase of creating an innovative drug. During the past 35 years, basic and clinical research in the pharmaceutical field have grown apart, creating a chasm in between, referred to as the valley of death (Butler 2008). In other words, as described in subsection 1-1-3, the valley of death in the pharmaceutical industry is defined as lying between upstream research on genes, proteins and biological pathways, and downstream research on potential drug candidates (Rai, Reichman et al. 2008), see figure 4 for the visualization of this "literature valley of death".

From another perspective, the fact that all drug candidates do not make it to become a drug that actually enters the market does not have to be negative. The valley of death is in this case serving as a natural selection phase, where only the ideas that are viable will survive (Girdauskiene, Venckuviene et al. 2015). This represents the nature of experimental research in medicine, where many candidates fail on the way. The result of this is that the innovative products that make it all the way have been critically studied and tested for their safety and efficacy (Edwards 2012). It can also be the case that the innovation phases are not sequential, but as Mimura, Cheng et al. (2011) describes it: *"Productive research and development collaborations often take place both in sequence and in parallel (...) more of a series of U-turns, switch backs, forked paths and potholes to be navigated simultaneously by several drivers"*. In an innovation process it is not always about that certain steps must be sequential, but rather that the product must pass through phases that are logical for its development, meaning that some activities also may be repeated (Markham, Ward et al. 2010).

Based on these definitions and interpretations of the valley of death, it is chosen to use another definition of valley of death in this thesis that excludes the basic research activities and includes activities closer to commercialization. The basic research activities are outside the scope of the model by Ortt and Schoormans (2004), making it a clearer scope for this thesis to leave them out. Moreover, the challenge to perform the right basic research and find an innovative idea is a complex process, which could be covered by another thesis research project on its own. This definition compared with the "literature valley of death" is also shown in the introduction chapter (figure 1-4), where the time period goes from the point

of invention until a first market introduction of a product. Using this definition changes the scope of the current literature in the pharmaceutical and biotech industry, and as some authors already mentioned: the period from when the clinical research starts until a market launch contains many activities and factors that also influence if the companies will successfully move a product to a first market introduction. A topic that can be researched separately is the translation of basic research activities, before the point of invention, into clinical applications. This area is chosen to not be included in the thesis, as explained in subsection 1-1-3, and therefore it is relevant to change the current definition of the valley of death.

Long time frame in the Valley of Death

The valley of death, as defined in this project, takes about 10 to 15 years to complete, where only the clinical trials and registration can take 10 years on its own (Reed 2011). This is confirmed by Hudson and Khazragui (2013), who states that the time span from filing a patent on a compound and the commercialization of the final drug is around 11 to 12 years, with a very small fraction of all created compounds to reach the final market. Frank, Sink et al. (1996) also tells the same story about the pharmaceutical industry, where bringing a new drug to the market is taking on average 12 years. However, the diffusion of high-technological products to the market from various industries can take all the way between 10 to 28 years (Ortt and Schoormans 2004), which means that 10 to 15 is a quite common time frame for radically new products.

Main goals to achieve in the Valley of Death

There are two main goals identified from the literature that companies should aim to achieve in the valley of death: (1) innovate new drugs, and (2) find sufficient funding, see figure 2-1. These goals will be further elaborated on in the following paragraphs.

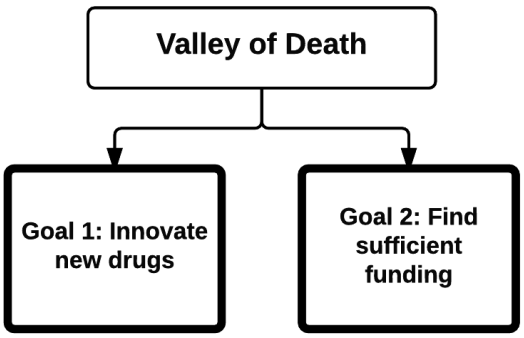

Figure 2-1: Overview of goals in the valley of death from the literature

Innovate new drugs

The pharmaceutical industry was once viewed as a growth industry with many exciting innovations being developed, and huge sales revenue from patented blockbuster drugs, but now

the pipeline of new medicines is drying up. As previously mentioned, the industry spending has increased while the number of new drugs, or New Chemical Entities (NCE), has decreased during the last 20 years (Sem 2014). Pharmaceutical firms have struggled with developing and producing fundamentally new small molecule drugs, particularly when it comes to work on drugs for new targets (Rai, Reichman et al. 2008). In order to find new potential patentable drugs, pharmaceutical firms have during the past few decades used the method of High-Throughput Screening (HTS) of small molecule libraries against target proteins. By using HTS, the firms can scan for a match between the molecule and a target protein in a very high speed, allowing for an increased efficiency. Unfortunately, the HTS has not yet resulted in an increased introduction of new drugs in the market (Rai, Reichman et al. 2008), but it might be a step in the right direction.

The current definition of the valley of death within the pharmaceutical industry is, as mentioned, between basic research and the start of clinical research. During the 1950s and 1960s the basic research activities were closely linked to the activities on the clinical side, however with the outburst of molecular biology in the 1970s, it started to change (Roberts, Fischhoff et al. 2012). The introduction of molecular biology led to the development of biomedical research as its own discipline, while the basic and clinical research started to disconnect from each other (Butler 2008). Compared with sectors based on engineering, the biomedical, biotechnology and chemical process industries are much more fragmented rather than integrated (Clark 2013). One of the reasons that the academia and the pharmaceutical firms are getting further away from each other is the conflict of interest regarding publishing of findings. Within academia, the scientists are striving to get their findings published in the high-level academic journals and rapidly share their knowledge. At the same time, the firms want to keep a competitive advantage towards the other firms, therefore frequently using non-disclosure agreements and keeping trade secrets (Coller and Califf 2009). Finding an optimal balance in this conflict is crucial to have collaboration between industry and academia (Rai, Reichman et al. 2008), and through this create new innovative products.

The process of translating discoveries from the basic research level into clinical research and testing to make products that will eventually benefit patients is called *translational research* (Roberts, Fischhoff et al. 2012). The focus of translational research is to carry it out while having improved health for the patient as the final outcome, therefore involving a long-term strategy that stretches further than the results of only the basic research (Wong 2014). Translational research, a rebranding of *clinical R&D* (Butler 2008), has during the last decades become a relevant topic to understand for policymakers because of the widening gap between the findings in basic research and the implementation in clinical research (Coller and Califf 2009). Pursuing translational medicine to bridge the valley of death has to be done in a team, where there are different roles and contributions for every member (Wong 2014), while still working towards the same goal.

Therefore it is relevant to understand how translational research can be done in order to improve the future healthcare. With the growing discipline of Systems Biology, defined as *"the analysis of the relationships among the elements in a system in response to genetic or environmental perturbations, with the goal of understanding the system or the emergent properties of the system"* (Weston and Hood 2004), changes to the future healthcare will be catalyzed. Through a deeper understanding of the system mechanisms, the genetics of the disease can be studied and the clinical trials adapted. Moreover, each patient can be analyzed to create personalized medicine, and predict the patient's reaction to a certain treatment

(Hamburg and Collins 2010). The innovation process of new drugs is heading more in the direction of personalized medicine, and this is something that both pharma and biopharma firms have to take into account when planning their innovation processes.

Find sufficient funding

The valley of death is in many articles seen as a financial gap (Roberts, Fischhoff et al. (2012), Frank, Sink et al. (1996), Hudson and Khazragui (2013)), due to a "chicken and egg" conundrum where manufacturers will wait for a demand in the market before starting production, and buyers wait for the product to be launched in the market before saying that they will buy it (Clark (2013), Williams (2004)). One possibility to get funding is in a pre-competitive stage, where a group of firms receive a first round of government funding to develop a technology into something applied. Most larger firms finance the coming steps with their own capital but for smaller firms, the subsequent round of funding comes from e.g. private investors, who want to see a promising product in the market before investing (Reed 2011). Due to this uncertainty, with risks that are hard to quantify regarding the product's potential success, debt financers are reluctant to invest in these projects that require large amounts of capital (Frankel 2012). With an average cost of $1 billion for taking a drug from idea to market (Roy, Taylor et al. 2009), and a time-span of 11-12 years from patent filing to its commercialization, it lies within the interests of many stakeholders to make sure that the drug candidates finally reach the market and can bring revenue. The innovation process in this phase includes a complex interaction with many stakeholders, leading to a lot of failures due to a lack of coordination between all stakeholders, with financing as a key constraining factor (Hudson and Khazragui 2013).

In order to ensure revenue, the pharmaceutical firms have long relied on patents for the so-called blockbuster drugs, which are drugs that produce high sales through large population segments. A common base in the business model for pharmaceutical firms has long been to produce blockbuster drugs, generating a lot of revenue that can be reinvested into new R&D (Carroll 2009). However, in the recent years many of the blockbuster drug patents have expired, falling off what has been referred to as the *patent cliff* (Sem 2014). To continue to be profitable, the pharmaceutical firms have to focus on developing drugs that work against new targets and can radically improve the current treatments (Rai, Reichman et al. 2008). The consequences of many patents falling off the patent cliff were that many companies lost market exclusivity and patented drugs became replaced with generic drugs. Overall, the revenue dropped and the pharmaceutical industry experienced the most comprehensive downscaling in history (Sem 2014). Opposed to the blockbuster drugs are the drugs for rare diseases, which have been seen as more unattractive products for the pharmaceutical firms to develop. This is mainly due to the small-sized population of less than 200.000 people that will buy and use the drug, therefore not generating revenue in the same way as the blockbusters (Sem 2014), even though the development costs are similar in amount. To inspire pharmaceutical firms to still develop these drugs, the Orphan Drug Act was introduced in 1983 in the United States, providing a favorable market exclusivity for developing drugs for rare diseases (Coller and Califf 2009). It also involved the opportunity to get a faster approval by the regulatory body, and therefore enter the market earlier (Frank, Sink et al. 1996). In Europe this protection for orphan drugs also exist, known as Orphan Designation (EMA 2016).

So, the two goals 'innovate new drugs' and 'find sufficient funding' were emphasized in the literature about the valley of death. The following paragraphs provide more details on what actors and factors are related to these goals, and how they are interconnected.

2-2-2 Results SQ2

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

The second sub question is about what actors and factors are involved in the valley of death, and how these affect the performance of companies. The literature revealed some different actors and factors, which are displayed in a table in appendix B. The findings are sorted in two columns; one for actors and one for factors. For each item, the different sources used to find the information are presented. All the identified actors and factors are mentioned in this subsection, where some are related to the main goals described in subsection 2-2-1, whereas others are relevant in the whole valley of death.

In order to make sense of all the identified actors and factors, they were grouped into logical categories, see table 2-2. The author made the grouping into these categories, since it was a logical way to cover all the different aspects from the findings. Moreover, it was possible to fit all actors and factors in these categories, indicating that they seem to be a suitable choice. The actors and factors are grouped into (1) Technology, (2) Skills, (3) Resources, (4) Planning & process, (5) Market, and (6) Regulations. The first category, technology, refers to factors that have to do with the technology or product that is being developed. In other words, this means different characteristics of the technology/product, e.g. product safety, or other things directly related to the technology/product. The second category, skills, is about different kinds of human capabilities and skills, e.g. communication skills. The skills in this category are relevant for the firm to possess internally during the valley of death. Following this, the third category, resources, have to do with different kinds of resources a company can have in the valley of death. Resources refer to e.g. capital or certain functional competences needed within the firm. This is different from skills, since a resource is a person/technology/function while a skill is something more abstract. The fourth category, planning & process, is about things that are connected with the operational part of the product development process. The difference with resources is that the planning & process category contains actors/factors on a higher level than a specific resource. In other words, planning & process refers to overall structures, plans or processes that are important in the valley of death. The fifth category, market, has to do with actors and factors that are present in the market around the biopharma company, e.g. external actors that influence the firm. This category also includes functional resources, but from a more external perspective than the category with resources. Here it is about getting input, advice or support from organizations or actors outside the biopharma firm. Finally, the sixth category, regulations, is concerning all formal rules, processes and authorities that a biopharma company must adapt to. The reason this category is needed is because the drug development process is very much steered and controlled by rules and regulations. Then it is clear to keep actors and factors related to regulations separately to enhance their importance.

Some of these different actors and factors can also be connected to the two main goals for companies in the valley of death, which are described in subsection 2-2-1. Below follows a

Table 2-2: Grouping of key actors and factors from literature into six categories

	(1) Technology	(2) Skills	(3) Resources	(4) Planning & process	(5) Market	(6) Regulations
Factors	Innovative idea	Leadership skills	Access to capital	Design of clinical trials	Market understanding	Regulations
	Cost-effectiveness of technology	Communication	Human resources	Access to patients		Intellectual Property regulations
	Commercial issues	Right skills & resources at right time	Information Technology (IT)			
		Commitment	Technological resources			
		Relevant knowledge & innovative capabilities	Support resources			
Actors			Investors		Patients	FDA
			Basic scientist		Physicians	Policymakers
			Clinician-scientist		Academia	
			Clinical scientist			
			Suitable partner			
			Entrepreneur			

short description on related actors and factors to the these two main goals, and following this there is a description of other actors and factors mentioned in the literature but not directly linked to the main goals.

Actors and factors for the goal 'innovate new drugs'

This paragraph explains the related actors and factors for the main goal to innovate new drugs. First, the actors will be explained together with factors that are related to a certain actor, and secondly the remaining factors will be explained. The actors that are involved in innovating new drugs are varying slightly depending on where the idea is generated. Many fundamentally new ideas are generated within academia, at research-oriented universities (Bessiere, Gomez-Breysse et al. (2014), Hudson and Khazragui (2013), Williams (2004)). Basic scientists are the ones carrying out the actual research at the early stage. The basic scientists can also be employed at a (bio)pharma company and then create the idea in that environment. The clinical scientists are needed to bring the idea further to clinical trials, and therefore need to communicate with basic scientists to transfer the idea to clinical practice (Roberts, Fischhoff et al. 2012), in order to achieve translational research and reach the patients (Wong 2014). In other words, this means having market understanding is crucial in order to know that the right product is developed (Coller and Califf 2009). Another actor that speaks both the

basic and clinical research language is a clinician-scientist, which is a medical doctor also pursuing basic research (Wong 2014). This actor can build bridges between basic and clinical scientists and potentially spur new innovations (Roberts, Fischhoff et al. 2012). Within a company it is important that an entrepreneur or other advocate for the idea with leadership skills, can speak up about the potential of the idea and inspire the company to go further (Frank, Sink et al. 1996). The study by Bessiere, Gomez-Breysse et al. (2014) shows that academic spin-off companies that experience growth have a more pronounced entrepreneurial orientation, favoring innovation and risk-taking. The innovative capacity has proved to be much more vital and dynamic within biotechnology firms compared with traditional pharma firms, resulting in a lot of new exciting innovations having their origin from biotechnology (Gans and Stern 2004). Thus, one key factor in innovating new drugs is to have an innovative idea to develop further into a final product that targets an unmet medical need (Coller and Califf 2009). Another key factor is that the actors involved need to possess relevant knowledge and innovative capabilities (Clark 2013), to bring the idea further. A final key factor is the regulatory environment from policymakers and Food and Drug Administration to which a company has to adjust and meet the criteria in order to create a new innovative drug (Frederickson 2012). The regulations are increasingly stricter (Hudson and Khazragui 2013), which makes the system even slower and can hamper innovation.

Actors and factors for the goal 'find sufficient funding'

For any company that wants to develop a new drug, a key goal is to make sure there is sufficient funding to go through with the project. As mentioned in subsection 2-2-1, government funding is one option to gain capital. A big pharma firm usually has internal capital and can allocate funds from their overall budget to new projects. However, for smaller or medium-sized biopharma firms the situation usually requires involving external investors to get funding ((Frankel 2012), Frank, Sink et al. (1996)). The obvious key factor in this activity is therefore access to capital. Another factor that can influence this is the Intellectual Property (IP) set-up that the company chooses, which can affect the sales revenue that the company exclusively can obtain (Rai, Reichman et al. 2008). Patents have long been a security for big pharma firms to secure sales revenue, especially on blockbuster drugs (Sem 2014). The investors are interested in how much potential sales revenue the company that they invest in can generate, which can depend a lot on the IP set-up.

Other important actors and factors

The systematic literature review also resulted in some other actors and factors that seem to be important in the valley of death. However, these do not really fit to the two main goals previously described, but they were described as having an importance in the valley of death. The actor 'suitable partner' is means that it is useful to find a partner with complementary expertise, e.g. an industry partner for pre-clinical studies (Coller and Califf 2009) or for support already in the early stage development (Hudson and Khazragui 2013). Suitable partner is therefore a broad term for an actor, and cannot be coupled to a specific goal. From the category 'technology', the factors 'cost-effectiveness of technology' and the 'commercial issues' are described as being important for the drug and its final product characteristics. The cost-effectiveness of a technology means considering the cost and effectiveness of the new

drug compared with current treatments. It is becoming an increasingly important factor, especially regarding the criteria the drug must pass to be approved in the market (Coller and Califf 2009). The commercial issues refer to being aware of competitors' products (Adams 2012) and having an early co-operation with key stakeholders to address potential commercial issues in time (Hudson and Khazragui 2013).

The factor 'right skills and resources at right time' is also connected to the factors human resources, support resources and technological resources. These are also overarching for the whole valley of death, since the companies will always need to have certain resources at certain times in order to go through with the development process (Markham, Ward et al. 2010). Human resources are the knowledge and capabilities available and accumulated within the company, support resources are e.g. academic incubators that provide knowledge and advice (Bessiere, Gomez-Breysse et al. 2014), and technological resources refer to having the right resources for the R&D, pre-clinical and clinical testing (Clark 2013). The following general factor is Information Technology (IT), which can provide the companies with easier and faster ways to handle large amount of data, e.g. from screening (Rai, Reichman et al. 2008). This is also a continuous resource that is needed and can therefore not be coupled to one of the two main goals. Finally, on the planning and process side, the design of clinical trials are important, and on the skills-side 'commitment' is also an important factor that cannot be connected to one of the key activities. Design of clinical trials is crucial in order to have a good process to carry out clinical activities. The design includes selecting a clinically relevant end-point to aim for (Adams 2012), and involving people with different expertise to create the design (Roberts, Fischhoff et al. 2012). The factor 'commitment' refers to an overall approach that the companies should have to get through the long and expensive drug-development phase (Coller and Califf 2009). Overall, the literature provided some examples of actors and factors that play a role in the valley of death, also with relation to the main goals described in the literature. The following subsection describes the interconnections between some actors and factors found in the literature.

2-2-3 Results SQ3

SQ3: *"How are the actors and factors in this phase interconnected?"*

As described in subsection 2-2-2, there are several key actors and factors involved in the valley of death; some directly linked to the main goals presented in the literature, and some others mentioned more in general. This third sub question did not generate a full overview of how all the actors and factors are interconnected in the valley of death. However, some relations between actors and factors were indicated in the literature. In order to get an overview of the important interconnections described both implicitly and explicitly in the literature, table 2-3 was created. This table shows an interpretation of the relations between actors and factors, some related to the main goals and some others. It should be emphasized that these relations were concluded based on the findings from the literature, and were not individually explicitly stated in the articles.

Currently there is a lack of a comprehensive overview of how the actors and factors mentioned in the literature are interconnected with each other. Therefore there is not a complete answer to this sub question from the literature, and the other research methods have to be used to find a more extensive answer.

Table 2-3: Author's interpretation of interconnections between actors and factors in main goals from literature

Main goal	Actors	Factors	Relation
1. Innovate new drugs	Academia, basic scientist, clinical scientist, clinician-scientist, entrepreneur, FDA, policymakers	Innovative idea, relevant knowledge & innovative capabilities, communication, leadership skills, regulations, market understanding	Basic scientists are mostly related to academia, and clinical scientists to companies. There must be communication between these actors, and an innovative idea together with relevant knowledge & innovative capabilities in order to innovate a new drug. The policymakers and FDA make the rules and regulations that the product must follow. The company benefits from having e.g. an entrepreneur with leadership skills internally.
2. Find sufficient funding	Investors	Access to capital, IP set-up	External investors can offer access to capital for biopharma companies. The IP set-up can influence how much sales revenue a company can get, which in turn can inspire the investors to invest or not.
Other actors and factors mentioned in literature	Suitable partner	Cost-effectiveness of technology, commercial issues, right skills & resources at right time, human resources, support resources, technological resources, IT, design of clinical trials, commitment	The suitable partner could potentially provide right skills & resources at right time, including all three types of resources mentioned.

2-2-4 Results SQ4

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

This sub question focuses on the strategies that the literature presented regarding the two main goals in the valley of death, i.e. how to deal with those situations and increase the chances of reaching the goals. There were also two strategies identified that targets other situations, and they will also be described in the end of this subsection.

Strategies targeting the goal 'innovate new drugs'

The first main goal, innovate new drugs, can be tackled with two different strategies from the literature. The first one is to use large-scale collaborations between industry and academia in order to develop new innovative ideas for drugs. In the paper by Rai, Reichman et al. (2008), a proposal of these collaborations is presented. Academia have expertise knowledge and skills in how to design assays that can identify promising targets, while the pharmaceutical firms own libraries of potential useful small molecules. The latter are usually trade secrets

of the firms, which is why collaboration is needed with the academia to create a win-win situation between the two actors through an exchange of knowledge. For these newer models of pursuing research in a collaborative way, it can also be seen that if industry, academia, funders of research, and the government are collaborating in the start of the project, the collaboration could have as much impact as possible on the outcome (Hudson and Khazragui 2013).

The second strategy to innovate new drugs is using multi-disciplinary teams. Since the complexity within science and innovation has increased, having only the traditional physician that understands the basic side is not enough. There is a need to develop multi-disciplinary teams including basic and clinical scientists, statisticians, bioinformaticians, industry experts and engineers to be able to create new, exciting innovations (Coller and Califf (2009), Butler (2008)). Additionally, knowledge about toxicology, pharmaceutical development, regulations and trial design are also necessary competences in these cross-competence teams (Roberts, Fischhoff et al. 2012). By having such teams, the different perspectives from each actor can be included in the process of pursuing more efficient translational research and drug development. According to Disis and Slattery (2010): *"Teams are effective innovators and are the most effective mechanism to translate discoveries made at the molecular level into measurable improvements in human health"*. Thus, collaboration can be a proposed strategy for companies, in order to get through the valley of death, since it is becoming more and more recognized that having different actors brings complementary knowledge to the table (Edwards 2012).

Strategies targeting the goal 'find sufficient funding'

For the second main goal, find sufficient funding, the literature proposes one explicitly mentioned strategy. Looking at it from a startup company perspective, Girdauskiene, Venckuviene et al. (2015) proposes to use crowdsourcing as a business model. Their definition of crowdsourcing is: *"Crowdsourcing is a type of participative online activity in which an individual, an institution, a non-profit organization, or company proposes to a group of individuals of varying knowledge, heterogeneity, and number, via a flexible open call, the voluntary undertaking of a task. The undertaking of the task, of variable complexity and modularity, and in which the crowd should participate bringing their work, money, knowledge and/or experience, always entails mutual benefit. The user will receive the satisfaction of a given type of need, be it economic, social recognition, self-esteem, or the development of individual skills, while the crowdsourcer will obtain and utilize to their advantage that what the user has brought to the venture, whose form will depend on the type of activity undertaken"*. This would be done with the idea to gain fund compensation and also knowledge, and therefore address both the financial issue and also potentially the skills and knowledge issue that can be present in a startup.

Strategies targeting other situations

In the article by Roy, Taylor et al. (2009), the suggestion of using "hit-to-probe-to-lead optimization strategies" to overcome the valley of death is presented. Normally the process to define what chemical compound to use for transforming a *hit*, a molecule matching the target

disease, into a *lead*, a developed drug candidate, has been a linear process with sequential steps. However, with the *industrialization* of the process, it is now possible to tackle several steps in parallel and therefore optimize the path from a hit to a lead. This is therefore a suggested strategy that pharmaceutical firms can use to overcome the valley of death, or more specifically to increase the speed of product development.

Due to patents expiring in the pharmaceutical industry, especially on the blockbuster drugs, there are opportunities to use the strategy of "drug repurposing" to take care of the knowledge from previous patents and bridge the valley of death. In other words, this means finding new uses for old and patented drugs, if a drug is discovered to also be suitable for treatment of another disease than it was originally developed for (Sem 2014). As the author expresses it: *"Quite simply, it will be easier for academic labs to traverse the drug development "valley of death" if they are repurposing, because repurposing will not require as many preclinical studies, which are typically areas of expertise for only industrial scientists"* (Sem 2014). This means that the amount of preclinical testing that needs to be done is reduced, providing an interesting option for firms to get faster to the market.

2-3 Conclusions

The literature review returned some answers to the different sub questions in the thesis, however at this point it is clear that other research methods are needed to complement the literature. The findings in the literature are more focused on pharma, but since the steps in the drug development process are similar for biopharma firms, the findings from the literature are also applicable there. The following two research methods, Vintura interviews and company interviews with biopharma firms, will contribute to the specific understandings of how the biopharma firms experience the valley of death, and potentially fill the gaps missing in the literature. The following paragraphs explain the answers per sub question.

The valley of death is described as a gap between resources, where more technical and scientific expertise is present on one side, and more marketing and commercial knowledge on the other side. It is primarily seen as a financial gap, but many sources are mentioning many other factors too, indicating that a better understanding of how this is all connected is needed. The literature is centered on two main goals in the valley of death: innovate new drugs, and find sufficient funding. One important remark is that the goal 'innovate new drugs' partly lies outside the scope for this thesis. This is due to the different definition of the valley of death that is used within the literature, where some pre-invention activities are included. The activity to innovate a new drug partly takes place before the valley of death starts, as defined in this report, with basic research activities to identify an innovative idea. That innovative idea is then used to enter the valley of death and try to develop a final product from. In other words, an assumption to enter the valley of death is that there already is an innovative idea. Through this logic, it is chosen to exclude the goal to innovate new drugs for further research in the thesis. Since the goal to innovate new drugs is excluded, it will also not be further elaborated on in this conclusion.

For the second sub question, about key actors and factors, six categories were identified: technology, skills, resources, planning & process, market, and regulations. The category with the most actors and factors is 'resources', providing an indication that the valley of death is

a very resource-intensive phase. For the main goal to find sufficient funding the investors and access to capital were described to be the key actor and factor to reach the goal. There were also actors and factors found that could not be coupled to that goal, but were still mentioned as important in the literature. These are indicating that there are other goals to be achieved in the valley of death, but that the literature is not explicitly discussing. For example, the factor 'right skills and resources at right time' is already saying that a company should aim to have talented persons as employees or collaboration partners.

In order to give an overview of the answers to the third sub question, regarding interconnections between actors and factors, table 2-3 was created to summarize the relationships. Although some connections were mentioned, a holistic view of the valley of death and the interconnections within this time period is missing.

The strategies presented in subsection 2-2-4 are not very elaborate on how to tackle the goal of finding sufficient funding. Many sources bring up this goal to be a key activity in the valley of death. However, the strategies on how to tackle it are not well described in the literature, thus the other research methods might generate more interesting strategies. Finally, there were two strategies mentioned, about hit-to-probe-to-lead optimization and drug re-purposing, that did not match a goal, once again indicating that the literature review could not on its own present all activities, actors, factors and strategies in the valley of death.

Chapter 3

Semi-structured interviews Vintura

In this part of the thesis, the knowledge level within Vintura is determined for the topic of valley of death in the biopharma sector. This is used as complementary information input next to the systematic literature review, providing a more practical approach. The interviewees were asked to answer the questions from a perspective of a (small) biotech or biopharma company, and not from a large pharmaceutical company point of view. This chapter describes the methodology of using semi-structured interviews, and presents the results per sub question, and finally the conclusion of these.

3-1 Methodology

In this section, the methodology for these interviews is explained. In order to assess the knowledge level of Vintura regarding this topic, the first step was to select whom to interview. The selection of the appropriate number of people to interview was made based on recommendations from the supervisors in Vintura, who could suggest who are knowledgeable in the area of the thesis topic. The selection generated five candidates to interview, where four are based within Vintura and one is from the external network of Vintura. The reason that the person from the external network is included is because it is an example of a valuable industry contact from Vintura, with a more funding-related perspective on the valley of death. However, this is not seen as a company interview, since the interviewee does not belong to a biopharma organization. These are the reasons to why this external interview is presented here in the Vintura chapter, and not in the company interview chapter.

The set-up for the interviews was semi-structured, meaning that the research questions were used as a main structure to follow, but there was also room to let the interviewee speak whatever came to his or her mind. The reason it was important to include some flexibility is because the thesis research is exploratory, meaning that there are many aspects of the characteristics of the valley of death that are still unknown. Therefore it not suitable to decide the exact interview set-up in advance, since there might be some aspects that the interviewee wants to add, which is why the set-up of the interviews was semi-structured.

The interviews were carried out in an open way, where the research topic was described shortly in the beginning, and the role that the interview plays in the thesis was described. Following this, the interviewee was asked to shortly introduce his or her background and experience in the pharmaceutical or biopharma sector. Then the different research questions were asked, one by one, with an open approach to let the interviewee tell broadly about the question in mind. The interview was ended with the interviewer providing a short summary of the main answers, and thanking the interviewee for his or her contribution.

For the last interview, a new interview set-up was used, as a pilot testing before using it with the biopharma firms. In this set-up, the interviewee was first asked an open question about how the valley of death looks like for biopharma firms, and what the main activities are. Following this, the interviewee was given a set of cards with all actors and factors identified so far in the research. The setting was decided to be any one of the sub phases (discovery/R&D, pre-clinical testing, clinical trials or launch preparation) and the interviewee was asked to select the key actors and factors and relate the cards on a white sheet of paper. This created a holistic visualization of how the actors and factors interrelate, and if some cards were missing, the interviewee was asked to add a new one. Moreover, the interviewee could also choose to not use certain cards in case they were not seen as key. Finally, strategies related to the interconnections were discussed.

After each interview, a summary of all the answers and discussions were sent to each interviewee to check if it was all correctly interpreted. This is the information that could be further used to answer the different research questions in this thesis.

3-2 Results

In this section the results from the interviews will be presented. The answers from all the interviews are split per sub question, and all the individual interview findings are combined into one answer. The full results per interview can be found in appendix E.

3-2-1 Results SQ1

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

In general, the answer to this question can be split up between what typical phase characteristics are, and which main goals the companies have to carry out in this phase.

Characteristics of the valley of death

The phase between invention and a first market introduction generally lasts about 10 to 15 years (V1, V4). The phase is uncertain and risky for biopharma companies (V2), since there are uncertainties about e.g. which product should be developed, how the firm should be structured, and how to get access to funding. However, initially there is little competition in the phase between biopharma companies, since the different companies are developing different products. Due to the intellectual property protection the firms can't develop exactly

the same compound, but if they later decide to use it for the same purpose it will be more competition between the companies (V1, V2, V4, V5).

Main goals in the valley of death

The Vintura interviews resulted in the identification of a total of five main goals to be achieved in the valley of death, as seen in figure 3-1. The main activities for the biopharma companies in this phase are connected to the drug development phases, e.g. the clinical phase, which are logical phases that they need to move their product through in order to launch it in the market.

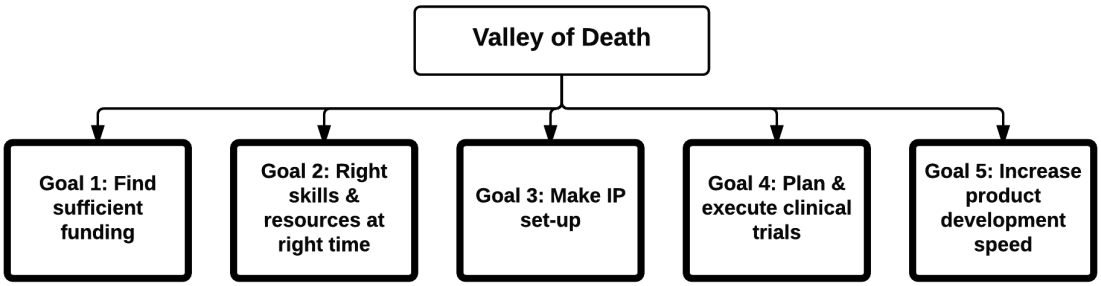

Figure 3-1: Overview of goals in the valley of death from Vintura interviews

The first goal described in the interviews is 'find sufficient funding', meaning that biopharma firms need to focus on having sufficient to get through the long and expensive valley of death. There is limited competition for funding between companies initially, since there is more capital available compared to great ideas (V2). However, there is a scarcity of investors with an appetite for very high risk (V2), and most investors become interested when the risk profile becomes more attractive (V2, V4, V5).

Secondly, the biopharma firm should aim to have the 'right skills and resources at right time' because the different sub parts of the valley of death require this. Four sub phases can be distinguished within the phase between an invention and a first market introduction. These are starting with R&D and development of a chosen target (the point of invention), followed by going through pre-clinical preparations, then carrying out the clinical trials, and finally apply for market authorization together with reimbursement and pricing approval (V1, V5). These sub phases require specific resources in order to get through the phase, and therefore the firms need to focus on having the right resources available at the right time, e.g. research facilities for carrying out R&D, or a suitable collaboration partner with experience in clinical trials. (V1, V2, V3, V5). This involves looking for a partner who can both support financially and help with clinical trials and market registration (V2, V3, V5). In this way, the access to capital and relevant knowledge could be combined. It is important to have a good network around the biopharma company, since if another path shows to be more promising, the biopharma firm can turn to its network for support (V4). This refers to another path to go in the product development, meaning that another version of the product or process has shown higher potential and the plans therefore need to be shifted accordingly.

The third goal is to 'make Intellectual Property set-up', meaning choosing an appropriate intellectual property set-up that fits the company and the specific technology or product (V1, V2, V5). It can be risky for a biopharma firm to reach out to a partner without having the idea protected (V2, V5). However, in the complex field of biopharma it is not really easy to copy an idea/concept, even if someone tells about it, since it is not so tangible in the beginning. Therefore, IP protection will be more critical when the biopharma firm starts defining the specific terms of a partnership, including determining ownership and revenue flows (V5).

Following this, the Vintura interviews highlighted a fourth goal to be 'plan & execute clinical trials'. The firms need to carry out clinical trials to test the drug candidate further. Before the clinical trials start, the firm needs to decide on what comparator to use in order to show the cost-effectiveness of the drug (V3). Setting up clinical trials usually requires that the biopharma firm seek support, due to the expensive and complex processes that needs to be carried out (V5). The clinical phase is more business-oriented than the previous research activities, and it's important that the research focus also transitions into thinking further towards launching a product in the market (V5).

Finally, the fifth goal is 'increase product development speed', because there is a constant challenge for biopharma firms to find out if some steps in the valley of death can be speeded up (V5), since it is an advantage to be first to the market with an innovative product. It is smart that the biopharma firm thinks ahead and keeps the end game in mind (V2, V5). Some steps are needed though, e.g. because of regulations, but working together with an external partner usually brings speed to the development process (V5). A few years before the launch the firm also needs to start thinking about the launch sequence of the drug, which more specifically means choosing what markets to target and when (V3).

Overall, the Vintura interviews brought up five main goals for the valley of death. In the following subsections, the related actors and factors are presented, together with a summary of their interconnections in table 3-2.

3-2-2 Results SQ2

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

The key actors and factors were split up using the same categories as in the literature chapter, in subsection 2-2-2. These categories and the related actors and factors are presented in the overview in table 3-1, with the number in the brackets showing the interview where it was mentioned. In the following paragraphs, the explanation per goal is given, presenting what actors and factors that belong to that specific goal. There is also a final section with actors and factors that do not fit to the five goals.

Actors and factors for the goal 'find sufficient funding'

In order for a biopharma firm to find sufficient funding, it usually requires an external actor to solve the key factor access to capital, since the firm usually doesn't have enough capital on its own (V1). One example of an actor that can provide funding is investors, e.g. private equity

Table 3-1: Actors and factors from Vintura interviews

	(1) Technology	(2) Skills	(3) Resources	(4) Planning & process	(5) Market	(6) Regulations
Factors	Innovative idea [2,3,4,5]	Leadership skills [2]	Access to capital [1,2,5]	Design of clinical trials [3,5]	Market understanding [4,5]	Regulations [3,5]
	Cost-effectiveness of technology [3,5]	Communication [1,2,3,4,5]	Human resources [2,5]	Access to patients [2,5]	Network around the company [2,4,5]	IP regulations [1,2,3,4,5]
		Right skills & resources at right time [1,4,5]	Technological resources [5]	Suitable organizational structure [2,4,5]	Large home market [2]	
		Professionalism & business sense [1,2,4,5]	Support resources [5]	Realizing when patent should be filed [1,3,4,5]	Market access criteria [3,5]	
		Relevant knowledge & innovative capabilities [1,2,3,4,5]		Decide on launch sequence [3]		
		Relationship mgmt. [2,3,4,5]		Well-defined business plan [4]		
		Self-awareness & self-criticism [2]				
Actors			Investors [1,2,4,5]		Patients [1,3,5]	FDA [1,3,5]
			Basic scientist [2,5]		Hospitals [1,3,5]	European Medicines Agency [1,3,5]
			Clinician-scientist [5]		Academia [1,2,3,5]	Policymakers [1]
			Clinical scientist [5]		HTA agencies [3,5]	
			Suitable partner [1,2,3,4,5]		Key Opinion Leaders [2,4,5]	
			Project manager [2,4,5]		Complementary technology providers [2,5]	
			Entrepreneur [2,5]		Big pharma firm [1,2,4,5]	

firms or venture capitalists (V1, V2, V5). In general there is a shortage of investors with an appetite for high risk, which means that the biopharma firm needs to have a convincing story (V2). It is also an option for a firm to reach out to academia and try to obtain grants, as a way to raise capital (V2). Reaching out to a big pharma firm can also be a way to get capital, together with support for e.g. clinical trial execution (V1, V5). When a biopharma firm wants to reach out to an external actor to raise capital, it is crucial to have skills in being professional and have a business sense (V2). In other words, it means knowing how to present the firm towards the outside world and knowing what information to share (V2).

Actors and factors for the goal 'right skills and resources at right time'

The valley of death requires the biopharma firm to have different skills and resources for carrying out various tasks and activities during this time period. It helps if the firm has an entrepreneur that can focus on creating and maintaining external contacts, preferably by having good relationship management skills (V5). Another factor that can positively influence the goal to have the right skills & resources at right time is finding support resources, e.g. business advice (V5). However, not having a good network around the company is a factor that can really hamper finding the right skills and resources (V4, V5). A strong network is critical in order to get the planning to work, since if another path in the drug development process seems more promising it is easier to be flexible (V4). Internally it is important that the firm has a good project manager with communication skills, because many things need to be aligned e.g. risk management and IP filing (V5). Especially, the project manager needs to be able to communicate the need of certain resources for activities during the product development phase (V5). Another blockage to find the right resources is finding a suitable partner that can provide the human resources needed (V3, V5).

Actors and factors for the goal 'make intellectual property set-up'

Making a suitable IP set-up is also a goal for biopharma firms in the valley of death, which means deciding on how to protect the project and/or process (V1). When a biopharma firm works with other partners it becomes relevant to decide about IP set-up (V5). It is critical for a project manager, in collaboration with regulatory affairs, to decide on when to file a patent (V1, V5). The timing of the patent filing is a critical decision point since a patent scope has a limit of 20 years (V1).

Actors and factors for the goal 'plan and execute clinical trials'

The clinical phase is very complex and requires a lot of planning in order to be executed well. It is valuable for a biopharma firm to get advice from Key Opinion Leaders (KOL) on how to set up the clinical trials and to make sure the product development is heading in the right direction (V2, V4, V5). KOLs are experts in the field, e.g. medical doctors in a certain area. In order to get an idea of what is used in the market, a clinician-scientist can also be brought in to find out about real-life situations and increase the chances of making successful clinical trials (V5). It is critical for a biopharma firm to consider the country-relevant market access criteria that the Health Technology Assessment (HTA) agencies use to evaluate the product

with before market launch (V3, V5). These need to be fully understood in order to make a good planning and execution of the clinical phase (V3, V5). The regulations from FDA (V5) and EMA (V3) create a barrier towards the planning and execution of clinical trials, due to the fact that a biopharma firm needs to adapt clinical trials design to the regulatory requirements (V3, V5). For the actual execution of the clinical testing, it is critical to have access to the right hospitals and physicians that can carry out the trials (V5). These actors bring access to patients, which are the study objects in the clinical trials (V2, V5). It is good if the biopharma firm plans well in advance in order to be able to work with the right hospitals, physicians and get access to the right patients (V2, V5), and the right clinical scientists that will do the actual work (V5). The crucial factor that ties all components together in the clinical phase is the design of the clinical trials, which should be designed considering the market access criteria (V5). There are many important choices to be made for the design, and having a good final plan makes a large difference in the execution of the trials (V5).

Actors and factors for the goal 'increase product development speed'

It is interesting for a biopharma to speed up the drug development process and get faster to market, since that can provide advantages such as being first to market, and enjoying the limited patent scope better (V1, V5). A crucial factor to be able to speed up is to have a clear and suitable design of the clinical trials (V5). By making the right choices in the design, e.g. how to compare the effect of the drug towards other patients, it might prevent the necessity of repeating certain steps and tests (V5). Bringing in the right complementary technology providers to get technological resources is also very important in order to speed up the process to market (V5).

Other important actors and factors

The interviews within Vintura also brought up some other actors and factors that at this stage cannot be coupled to one of the five main goals that were described. The factors 'innovative idea' and 'relevant knowledge & innovative capabilities', together with the actor 'basic scientist' are all belonging to the goal of creating an innovative idea for a drug. As described in the literature chapter, this activity partially takes place before the start of the valley of death for this thesis. This means that these factors and the actor will not be further discussed anymore, since they are outside of the scope for this thesis project.

Two factors were mentioned to be important in general for a biopharma firm: the first one is a well-defined business plan (V4), and the second one is suitable organizational structure (V2, V4, V5).

Other factors that were described as important are cost-effectiveness of technology, because the technology needs to be better than existing treatments (V5). Two other factors are leadership skills and self-awareness & self-criticism, which are two kinds of skills needed to be able to develop the right product (V2). Finally, the factor 'large home market' was mentioned to have a positive influence on a biopharma firm when choosing what product that should be developed (V2). Table 3-2 provides an overview of all actors and factors, both from the main goals and the additional ones.

3-2-3 Results SQ3

SQ3: *"How are the actors and factors in this phase interconnected?"*

Some interconnections between actors and factors in the valley of death were described in the Vintura interviews. The previous subsection contains descriptions of what actors and factors belong to the main goals, and in table 3-2 there is an overview and short description of these interconnections. On the basis of all the information from the Vintura interviews, the author made the interconnections in this table, by interpreting explicit and implicit information.

Table 3-2: Author's interpretation of interconnections actors and factors in main goals from Vintura interviews

Main goal	Actors	Factors	Relation
1. Find sufficient funding	Investors, academia, big pharma firm	Access to capital, professionalism & business sense	Access to capital can be obtained from investors, academia or big pharma firm. The skill 'professionalism & business sense' is needed for a biopharma firm to reach out to external actors to raise capital.
2. Right skills & resources at right time	Entrepreneur, project manager, suitable partner	Relationship mgmt. skills, support resources, network around company, communication skills, human resources	Relationship mgmt. skills are connected to the entrepreneur, who can then create and maintain a network around the company. Communication skills belong to the project manager. A suitable partner can provide human resources to the firm.
3. Make IP set-up	Project manager, regulatory affairs	Realizing when patent should be filed	The project manager together with regulatory affairs should make the decision on when to file a patent.
4. Plan & execute clinical trials	KOLs, clinician-scientist, clinical scientist, HTA agencies, FDA, EMA, hospitals, physicians	Advice, market access criteria, regulations, access to patients, design of clinical trials	KOLs and clinician-scientists can provide advice, which can lead to a better clinical trials design and execution. Market access criteria from the HTA agencies have an influence on how the design of clinical trials should be done. The hospitals and physicians provide access to the right patients. FDA and EMA are setting the boundaries of the clinical trials with their regulations.
5. Increase product development speed	Complementary technology providers	Design of clinical trials, technological resources	Complementary technology providers can contribute with technological resources needed to speed up the development.
Other actors and factors mentioned in Vintura interviews	-	Cost-effectiveness of technology, well-defined business plan, suitable organizational structure, leadership skills, self-awareness & self-criticism, large home market	No clear relation between these factors was described.

Moreover, the Vintura interviews also resulted in a few visuals of some interconnections in the valley of death. From one interview (V2), the interviewee defined a set of interconnections, which is shown in figure 3-2. The interviewee emphasized that a great idea and a skilled entrepreneur are key elements in order to have a successful innovation. It is clear that a good idea is needed to have a successful product in the market; to secure that potential revenue can be obtained. A skilled entrepreneur is the person or group that can manage to communicate the benefits of the idea towards the internal organization or towards external parties. However, if any of the other three components, capital, talent and organization, are missing there will also not be a successful innovation. There is a need for capital in order to finance the product development process, a need for talent to have the right competencies, and a need for a functional organization in order to bring a product to the market. All of these components mentioned are related to a company, which in itself is present in an external environment also shown in the illustration.

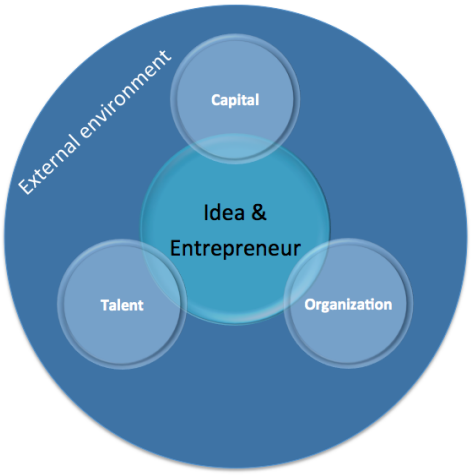

Figure 3-2: Interconnections from interview V2

Finally, another interviewee (V5) defined some interconnections using the cards of actors and factors in the new interview set-up described in section 3-1. First, the interviewee described interconnections in the discovery/R&D sub phase of the drug development process, with keeping the biopharma firm as the central starting point (see figure 3-3). This discovery/R&D sub phase is the first part of the valley of death, as seen in chapter 1, figure 1-5. The most important interconnections from this interview have already been discussed in table 3-2.

The last sub phase that was discussed in the fifth interview was the clinical trials sub phase, where the interconnections can be seen in figure 3-4, and have also been highlighted in table 3-2. This clinical sub phase is a part of the valley of death, as seen in figure 1-5 in chapter 1. In general, this phase is about moving away from the R&D setting towards a more business-oriented environment, the closer the commercialization gets.

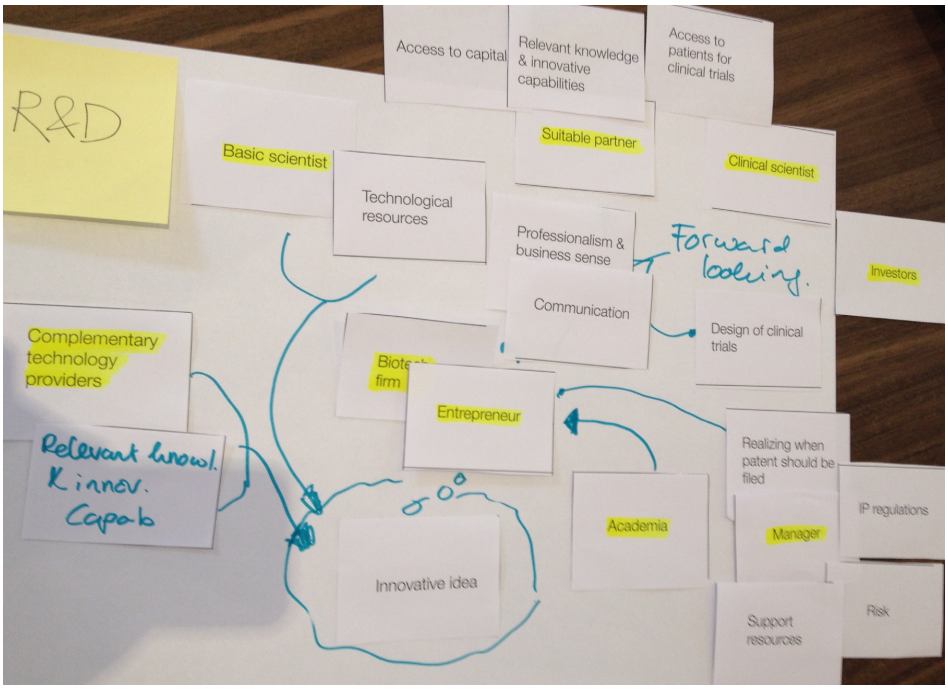

Figure 3-3: Overview of interconnections in the discovery/R&D sub phase in the valley of death (V5)

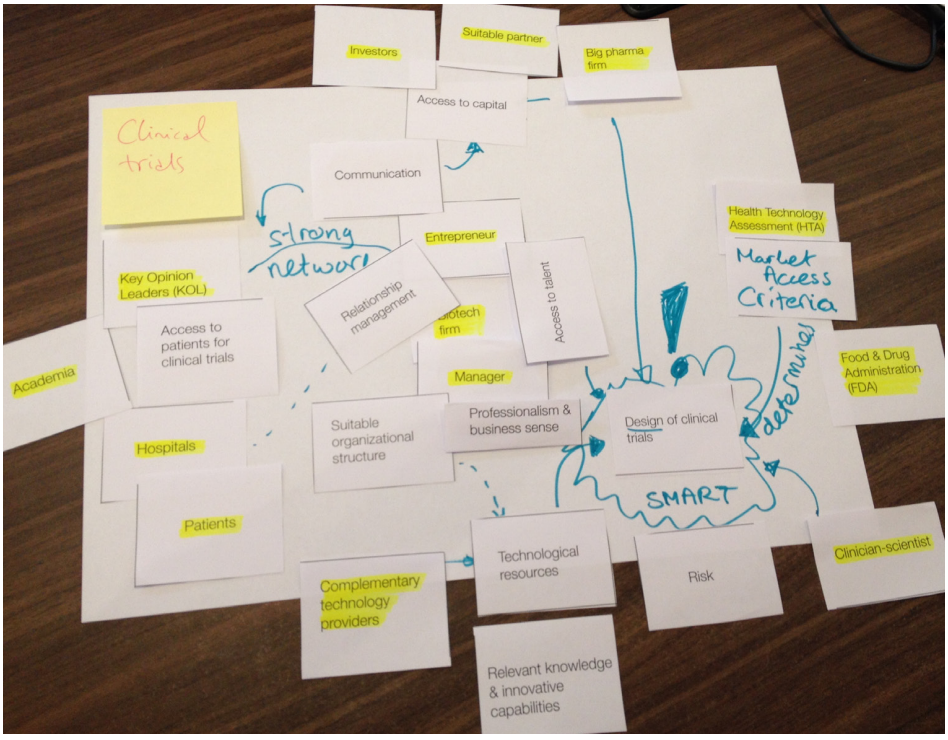

Figure 3-4: Overview interconnections clinical trials sub phase in the valley of death (V5)

3-2-4 Results SQ4

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

The different Vintura interviews resulted in a set of recommended strategies for companies to use in this phase. First, the strategies targeting the main goals will be presented. After that, some strategies targeting other situations will be described.

Strategies targeting the goal 'find sufficient funding'

From the interviews there were strategy suggestions for all of the five main goals mentioned. For the first goal, find sufficient funding, there were four strategies presented. The first one is to make sure to have a strong person internally that can reach out to and communicate with investors, in order to deal with the need for professionalism and business sense skills (V1, V2). The second strategy is to seek investors that bring in knowledge and network, in order to both get access to capital and also to knowledge relevant for the product development (V2). The third strategy is to reach out to academia for grants (V2), and finally the fourth strategy is to make sure risk-profile is interesting for big pharma to invest (V5). The last strategy is valid for the situation when a biopharma firm wants to reach out to a big pharma firm for capital.

Strategies targeting the goal 'right skills & resources at right time'

The second goal, right skills & resources at right time, also received three strategy suggestions from the interviews. Number one is to reach out early to key stakeholders, in order to make sure that the right contacts are established in time for when the actual need of a specific skills or resource appears (V2, V3). Secondly, the strategy to combine parties with overlapping network was suggested, to solve the need of having a good network around the company (V4). Thirdly, find a partner that covers the lack of expertise needed was proposed in relation to the blockage that a lack of suitable partner could be (V5).

Strategies targeting the goal 'make intellectual property set-up'

Following this, the third goal is to make an IP set-up, which was targeted with one strategy. The strategy is to file patent as late as possible to maximize the use of the patent scope (V5). From an acquisition point of view, this is important since the investors usually value the remaining patent scope highly (V5).

Strategies targeting the goal 'plan & execute clinical trials'

The next goal, plan & execute clinical trials, received three strategy suggestions. Number one is to understand market access criteria that HTA agencies are using to evaluate the final product (V5). In that way, the firms know how to plan and adapt the execution of the clinical trials and increase the chances that the final product meets the criteria (V5). Secondly, the next strategy is to design the clinical trials according to market access criteria (V5). Finally,

the third strategy is to include the right comparator in the design of clinical trials (V3). This is important in order to make sure that the developed product can be compared to a relevant similar product (V3).

Strategies targeting the goal 'increase product development speed'

The fifth and final goal, increase product development speed, received four strategy suggestions. Number one is the same as for goal 3; find a partner that covers the lack of expertise needed (V5). Using this strategy can therefore not only bring more resources and skills, but also contribute to a faster development speed. Secondly, use capabilities of partners to speed up the development is a strategy that focuses on letting a partner carry out certain tasks if they are better at it (V5). The third strategy is to design the clinical trials according to market access criteria, which was also mentioned in the previous goal. The reason for this is because both of these goals have the factor 'design of clinical trials', but in this goal it is about saving time and not about carrying out the clinical trials in the best way, although these are closely connected. Finally, the fourth strategy is also the same as in previous goal, to include the right comparator in the design of clinical trials (V3). Once again, the focus of this goal is to save time, but this strategy contributes positively to both this and the previous goal of 'plan & execute clinical trials'.

Strategies targeting other situations

From the Vintura interviews there were also four additional strategies proposed that are connected to how biopharma firms should behave in the valley of death. These strategies cannot yet be coupled to a specific goal in the valley of death. The first strategy is to bring in relevant experts on day 1 in order to be aware of important things from the outside world at an early stage in development, e.g. market access criteria (V4). The next strategy is to be forward-looking in the approach, meaning that the firm always has to think further to the next step and the implications for the future of making a certain decision (V5). Following this, the third strategy is to go for the most difficult questions first, meaning that it is important to face potential challenges early on to make sure the product development is heading in the right direction (V2). Finally, the fourth strategy is to communicate well between company departments, which refers to that it is important to take care of all expertise and knowledge within a firm to make sure the firm is heading in the right direction (V3).

3-3 Conclusions

The interviews within Vintura have contributed with a more practical perspective towards the different sub questions compared with the systematic literature review. Overall, the sub questions got much more extensive answers here, making the findings a good complement to what the literature could present.

The phase between an invention and a first market introduction is in general risky and uncertain for biopharma companies. The first sub question generated a total of five main goals that are relevant for companies traveling through the valley of death: find sufficient funding, right

skills & resources at right time, make IP set-up, plan & execute clinical trials, and increase product development speed. It is not yet clear if these are all the important goals in the valley of death, which has to be established through the company interviews with biopharma firms.

The second sub question generated quite a large table with key actors and factors, where most of them were from the categories 'resources' and 'market'. The majority of the actors and factors could be coupled to the five main goals, however there were also some other actors and factors that could not be coupled. That is an indication of that there might be more goals in the valley of death where these belong.

Some interconnections were presented for the third sub question, with an overview in table 3-2. The Vintura interviews also returned some visualization of the interconnections that are valuable in understanding the mechanisms in the valley of death.

Finally, the fourth sub question got a set of strategies linked to all the five goals presented from the findings. The strategies are all very concrete suggestions on how to deal with certain issues in the valley of death from a company perspective. There were also some additional strategies that not yet could be related to the main goals, confirming the indication that further research is needed to make sure the main activities in the valley of death are well understood.

Chapter 4

Conclusion on findings from the literature and Vintura interviews

In this chapter the main conclusions from the systematic literature review and the semi-structured interviews in Vintura are presented. First there is a short introduction about the conclusions, and then the conclusions per sub question are presented with the comparison of results from both the literature and interviews in terms of agreements and disagreements. Following this, potential gaps are identified where there is currently not a complete answer yet. Finally the focus points for the company interviews are explained in the last subsection.

4-1 Introduction

At this point of the research, two out of three of the different parts of the research have been carried out. This has resulted in some findings that will be further analyzed in section 4-2, divided per sub question. The literature has generated findings from the past decades, with finding applicable both in the pharmaceutical industry as well as the biopharma industry. The Vintura interviews have provided a more practical approach with more focus on the biopharma industry. There is not yet a comprehensive picture of how the valley of death looks like for companies, however these two research methods provided a good base of knowledge to which the company interviews provided additional knowledge from a more practical perspective.

4-2 Conclusion of findings from literature and Vintura interviews

In order to conclude the findings from the literature and Vintura interviews, the respective conclusions will be presented per sub question. Following each sub question there will be an analysis on whether there are points of agreements or disagreements between the findings.

4-2-1 Results SQ1

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

Agreements

Both the results from the literature and the Vintura interviews are describing the valley of death as a gap between resources. The literature describes it as having more technical resources on one side of the valley, and more commercial resources on the other. Within the pharmaceutical industry it is described to be a knowledge gap between basic research and clinical research, which is a sort of resource gap as well. In the interviews it was explained that the companies are in need of certain resources to make it through this phase, and the need varies over the whole valley of death. In other words, the companies need different resources at specific time periods.

The findings also overlapped regarding the general phase characteristics, that the valley of death is a challenging and uncertain time period for the companies. It is also a risky phase where external investors can be reluctant to invest too early because of uncertainties that cannot be quantified regarding the potential success of the product, both from a technological and market perspective. Also the time frame, 10-15 years, was mentioned both in the literature and in the interviews.

Disagreements

The literature points out the valley of death to primarily be seen as a financial gap, while the Vintura interviews were emphasizing that it is important to have the right resources at the right time. This not only involves access to funding, but also access to the right skills and knowledge. The major disagreement is concerning what the main goals in the valley of death are for companies. The literature only pointed out two goals, where it also turned out that one of these goals lies outside the scope of the definition of the valley of death in this thesis. As a contrast, the Vintura interviews generated in total five main goals that companies should try to solve in the valley of death. The one goal from the literature is the same as one of the five goals from Vintura, so a total of five identified goals can be concluded after these two research methods. Moreover, one of the goals from the Vintura interviews is 'right skills & resources at right time', which was mentioned as a factor in the literature. The difference is that the literature did not bring up enough information around it for it to be considered a main goal, as opposed to in the Vintura interviews.

4-2-2 Results SQ2

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

Agreements

The different categories of actors and factors; technology, skills, resources, planning & process, market, and regulations, were present in both the literature and interview findings. This shows that there is an understanding that several perspectives play a role in this phase, even though it is still not clear how they relate or if some are more important than others. Both research methods generated information about actors and factors related to the main goals. The goal 'find sufficient funding' was presented in both of the research methods, and both described similar actors and factors related to achieve this goal. Both of the research methods also describe some actors and factors that do not seem to fit with a main goal, but still are important in the valley of death.

Disagreements

The literature findings present a shorter list of actors and factors compared with the Vintura interviews. The Vintura interviews describe the most actors and factors in the categories skills, resources, and market. Due to the practical nature of the work done within Vintura, it is also logical that the market perspective around a company is more covered than in the literature.

4-2-3 Results SQ3

SQ3: *"How are the actors and factors in this phase interconnected?"*

Agreements

Neither the literature nor the interviews show a comprehensive overview of how all actors and factors are interconnected in the valley of death. This became clear from table 2-3 and 3-2, which show some interconnections, but not completely an overview with all involved actors and factors in the valley of death. Therefore it is an indication that the answer to this sub question is not yet complete. Both in the literature and in the Vintura interviews the interconnections regarding the main goal 'find sufficient funding' were similar.

Disagreements

The literature did not contribute with any visual overview of interconnections, only the interconnections described in words in table 2-3. Two Vintura interviews contributed with some visualization of interconnections. One picture was created in the second Vintura interview and is shown in figure 4-1. It was stated by the interviewee that all of these factors and actors were needed in order to create a successful innovation. If one of these elements were missing it would not result in a successful innovation. However, the activity to create an innovation lies outside the scope of this thesis, but the visualization still points out some important elements for the valley of death, in terms of capital, entrepreneur, organization and talent.

From the last Vintura interview, two pictures were created with overviews of some interconnections. This is the result from using a different interview set-up, as previously explained in

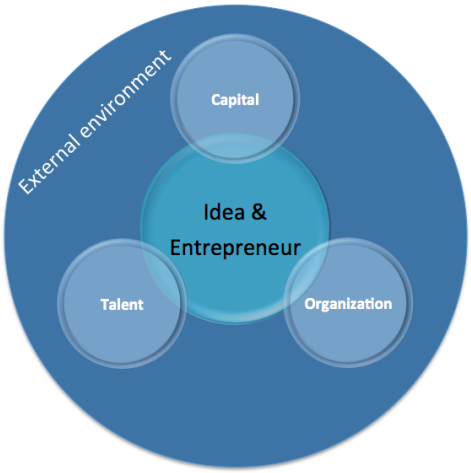

Figure 4-1: Interconnections from one Vintura interview (V2)

section 3-1. These two pictures are shown in figure 3-3 and 3-4. The interviewee described the clinical phase as the most complex one, with many interconnections between actors and factors. This final interview resulted in the most comprehensive visual overview of the interconnections between actors and factors so far in this thesis, but table 3-2 describes more in detail the relations from all the Vintura interviews together, based on analysis from the thesis author.

4-2-4 Results SQ4

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

Agreements

Both in the literature and in the Vintura interviews there were strategies proposed for each of the main goals that were brought up in respective research method. Both methods gave rise to an additional number of strategies that currently cannot be coupled to one of the identified main goals.

Disagreements

There were some differences in the choice of strategies within the literature and interview findings. The Vintura interviews brought up many more alternative strategies per goal, providing the opportunity for choosing a different approach. The literature was very limited in describing strategies, and the Vintura employees have much more practical experience within strategy setting, resulting in many answers.

4-3 Identification of gaps

In order to identify knowledge gaps that still exist after these two blocks of research, some comparisons were made between the findings from the literature and from the Vintura interviews. The previous section described the agreements and disagreements of the findings, however some sub questions were answered more complete than others.

As seen in the sections above, there is a lot of information found from both the systematic literature review as well as from the semi-structured interviews in Vintura. Currently the first and second sub questions have received quite some information in order to answer these, especially a lot of different actors and factors listed.

However, what is lacking so far in the research is to have a more holistic view on the interconnections between these identified actors and factors. This was therefore seen as a gap that needed to be further investigated through the use of company interviews.

Regarding the fourth sub question about the strategies, it was also interesting to focus on this during the biopharma company interviews. This was done in order to get the practical approach from the companies on how they "hands on" deal with this phase is good in order to understand what is used in practice.

4-4 Defined approach and focus for biopharma company interviews

Since it would be valuable to understand the interconnections better, it was decided to use cards with actors and factors identified from previous research in this thesis and ask the interviewees to relate them as done in the last Vintura interview described in section 3-1. The pilot testing of this method was done for the last Vintura interview, and the outcome was positive because the interviewee said it was clear and structured and the interview generated results that could be used further. In order to not miss out on any new actor and factor it was also possible for the interviewee to add more actors and factors if he or she believed that some are missing.

Regarding the strategies it would be good to ask this in the end, when all the rest is already discussed, so that the companies can explain how they dealt with these kind of challenges. Some strategy suggestions will probably be implicit during the interviews, but it is important to ask explicitly for explanations on these. In order to get a more comprehensive story from each company, it was decided to make two interviews per company.

Chapter 5

Biopharma company interviews

This chapter describes everything related to the biopharma company interviews that have been carried out during the thesis research. The company interviews are a part of the full thesis and are separately presented here. First, the company interviews are introduced and shortly explained in the introduction. Second, the specific methodology for these interviews will be described. Following this are four subsections, one for each of the four companies, describing the company shortly and the results from the two interviews per company. Finally, there is a cross-analysis in the last section, where the results from all four companies will be added together and further analyzed.

5-1 Introduction

Exploring and understanding the valley of death can be done in several ways, with various approaches to find answers. Since the current literature on the valley of death and its characteristics is very limited, it is valuable to add some real-world experiences from the biopharma field, e.g. by using case studies. According to Eisenhardt (1989), a case study is *"a research strategy which focuses on understanding the dynamics present within single settings"*. There can also be different levels of analysis within a case study, e.g. looking at an industry level or firm level (Eisenhardt 1989). There are different aims that can be accomplished using case study research: test theory, provide description, or generate new theory (Eisenhardt 1989).

However, for this thesis it was decided to make company interviews instead of pure case studies, but still with the aim of using the outcomes to generate new theory on the valley of death. These biopharma company interviews were added to this thesis research, with the hopes to create a complementary source of information to add to the findings from literature and from the Vintura interviews. As previously explained, all the research questions could not be fully answered by only using the literature and the Vintura interviews. The company interviews consisted of in-depth interviews with four biopharma companies, two smaller and two larger companies, where small refers to a few hundred employees and large a few thousand. Within each company, two separate interviews were conducted, resulting in a total of eight interviews.

5-2 Methodology

For this thesis research it was chosen to use company interviews as one method to find answers to the research questions. The methodology seemed to fit well to find answers to "how-questions" and for exploratory research, which are two reasons for why this method was selected. This section describes the methodology for the company interviews in the thesis including: the chosen interview set-up, how the set-up can generate answers to the research questions in this thesis, the strengths and weaknesses with the set-up, and finally the selection of companies.

Interview set-up

In this research, the purpose is to explore and increase the understanding of the valley of death, where a key assumption is that there are more factors than only financial shortage that plays a role in this phase. In order to find other actors and factors in the valley of death than financial shortage, in-depth interviews were used to gather information from the biopharma companies. The method was, as also described in section 3-1 for the last Vintura interview, to use a semi-structured interview set-up. Initially, the interviewees were asked an open question about how the phase between the point of an invention until a first market introduction, the valley of death, looks like for a biopharma firm. It is an open question where the interviewee can tell some general characteristics about the phase, and explain some key activities or goals that are relevant here. Following this, the interviewee was presented with cards, each stating one actor or one factor identified from previous research methods. The task for the interviewee was to first choose a focus on one or two sub phase(s) in the valley of death (discovery/R&D, pre-clinical testing, clinical trials, or launch preparation), and then explain how selected key actors and factors relate to each other here. The reason that the interviewee was asked to choose a focus area was due to the time constraint during the interview, in combination with having an exploratory research with quite a broad scope. Moreover, since the valley of death spans several activities over a time period of a decade, it is common that the company employees have more knowledge and expertise in a particular area of the broad valley of death. Having a number of eight interviews in total compensated to cover all sub phases in the valley of death to some extent. Each interviewee was asked to place the cards with the most critical actors and factor on a large paper sheet and explain how they relate to each other, either only verbally or by drawing connecting lines. In addition, if the interviewee thought an actor or factor was missing, a new card was created to add to the number of actors and factors identified. These new cards were then also used for the subsequent interviews. There was also the option for an interviewee to exclude cards that were not seen as important. Finally, the interviewee was asked to explain various strategies that can be used to better deal with the valley of death and increase the chances of successful market introduction of a new product.

After the execution of each interview, the information was reduced to become a structured and readable story. This meant cutting out information that was not relevant for the research questions, and summarize the remaining information into a logical story. Finally, each interviewee checked these summaries before the information was used further in the thesis work.

Generation of answers to research questions

The interview set-up was created to fit with the research questions for the thesis project. It was also created in order to get the most out of the interviews within the limited time frame of each interview. The first question from the interviews generated an overall description of the valley of death that could be used to answer the first sub question in the thesis, regarding how the biopharma companies experience the valley of death. The following question in the interview set-up was asking the interviewee to select the key actors and factors from a set of cards, and also visualize their relationships. By doing so, the interviewee provided information for answering both the second and third sub questions in this thesis, about key actors and factors and their interconnections. Finally, the interviewees were asked about specific strategy suggestions to get through the valley of death, which was used to answer the fourth sub question about strategies. Overall, the semi-structured set-up was a way to generate answers to the research questions within the limited time per interview.

Strengths and limitations of the interview set-up

The interview set-up used for the biopharma company interviews offered both strengths and had certain limitations. These will be shortly elaborated on here, and further discussed in the chapter 7, subsection 7-6-1.

The strengths of using the interview set-up as described are that the findings quite easily could be translated to answers for the four sub questions used in this thesis. Both flexibility and stability were offered in the structure of the interview set-up, since there was room for the interviewee to add information around the topic of the valley of death, but also to follow the structure of the questions and create a logical story. Using ready-made cards with actors and factors was an efficient way to maximize the use of the limited time scope within each interview, since unnecessary time did not have to be used for repeating actors and factors that were already known from previous research methods. Instead, the focus could be on understanding interconnections and strategies that were less evident in the previous research.

However, there are also limitations with the interview set-up used. The structure in the interviews could potentially generate bias since the interviewer was focusing on the questions that were planned beforehand to contribute to the answering of the thesis research questions. This might mean that the interviewer steered the interviews in that direction, and that other valuable information about the valley of death was missed. In the process of making each interview summary, it could be that information was cut out that still contribute to the knowledge of the valley of death, but not specifically for this thesis focus. Following this, another limitation is making general conclusions from results of a set of eight interviews. However, this is a general concern from performing research on a selected number of companies or cases, and should therefore not be seen as a blockade towards making a scientific contribution.

Selection of companies

The selection of companies for this thesis research was chosen to be biopharma companies, in order to expand the view within the current literature, which is mostly focusing on large traditional pharma. Due to the focus of the thesis on biopharma, and the current trends

and changing industries, the biopharma firms were seen as suitable study objects. One criterion was that the companies should either be Dutch, or at least have part of their business operations in the Netherlands. It was chosen to include two smaller, with a few hundred employees, and two larger, with several thousands of employees, biopharma firms in order to get a better coverage, and to find out if the small and large firms experience the valley of death in the same way. Two interviews were conducted per company, resulting in a total of eight individual interviews, referred to as interview B1, B2, B3, B4, B5, B6, B7, and B8. The full interview summary per interview can be found in appendix F.

5-3 Company 1

The following section consists of two parts where the first one describes the company and the interviewees, and the second one presents the interview results per sub question.

5-3-1 Description Company 1

The first company is a small, biopharma company (company 1) with between 50-100 employees, where the majority is working in the Netherlands. Focus area for the company is to target rare diseases by the use of protein products (biologics). Currently the company has one product that is launched in the market, both in the U.S. and in Europe, and several other products in the development pipeline, where the majority currently is in the non-clinical phase. There are competitors on the market that produce the same protein, but using a different production process that is more risky than the one company 1 is using.

The two persons interviewed in company 1 have different positions in the company, where interviewee "B1" is working in clinical development, and interviewee "B8" is having a management position. From interview B1, the interviewee was able to share a lot of valuable information regarding the clinical sub phase of the valley of death, one of the sub phases described in chapter 1, figure 5. The interviewee works in clinical operations on a daily basis and could therefore provide explanations of what actors and factors are involved in the clinical work. From the other interview, B8, the interviewee could provide a more general view on the valley of death, since having a management position provides such a perspective. The interviewee also shared information about what company 1 did right in order to be successful and survive the valley of death. Finally, the interviewee explained what happens in the discovery and R&D sub phase by using the cards with actors and factors. These two interviews therefore complemented each other and provided insights from both the discovery and R&D as well as from the clinical sub phases in the valley of death.

5-3-2 Results Company 1

The results from this company come from two interviews, which are B1 and B8. The following text contains the results per sub question in the research.

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

Characteristics of the valley of death

From this company, the valley of death is described to have a time frame of around 10 years (B8). The phase between an invention and its first market introduction is described as a risky phase for companies, so overall risk management is needed in the company. It is also possible to share the risk by collaborating with partners (B8). The company should also be aware of risks related to their products and related to potential operational barriers (B1).

Main goals in the valley of death

In total, the interviewees brought up five main goals that are relevant for biopharma firms in the valley of death. These will be shortly elaborated on in the following paragraphs. An overview of all the goals from the interviews in company 1 can be seen in figure 5-1.

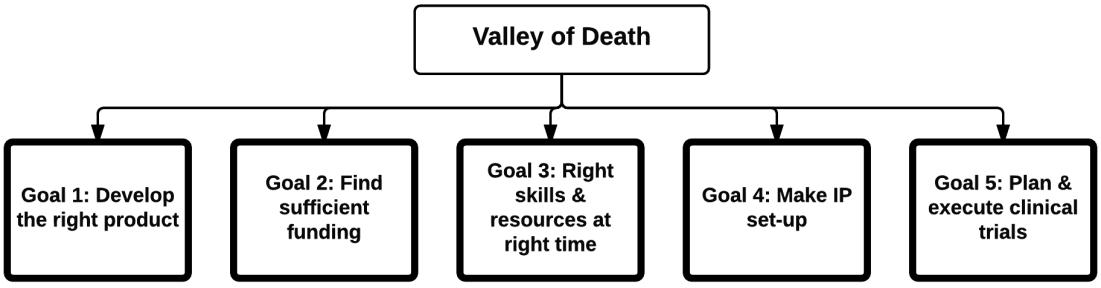

Figure 5-1: Overview of goals in the valley of death from company 1

The first goal is to develop the right product, which means that it is not only enough to have an innovative idea but it should also be the right product in terms of market and patient needs (B1, B8). A long-term thinking, and already at an early stage, is needed in order to set the right goals for the product development (B1). When an idea is developed further into a product, it is important to make sure that the final product will be better than current treatments in the market (B1, B8).

Find sufficient funding is also a main goal in the valley of death since there is no sales revenue from the new product in this phase (B1). There must be sufficient capital for the R&D and further development of the idea (B1). It is crucial to manage the financial situation in order to survive the long and expensive phase (B8).

Thirdly, a company needs to make sure to have the right skills and resources at the right time. This is something that is continuously needed over the whole valley of death (B8). Access to talent is important for the company, and there is a need for suitable persons for the job that can communicate and are willing to learn new things (B1).

The fourth goal is to make an IP set-up, since the company needs to decide on this especially when working with partners and setting up contracts of IP ownership (B1). A suitable IP set-up is needed in order to not risk losing exclusivity on the idea (B8).

Finally, plan & execute clinical trials is a critical goal because the clinical phase is complex and includes many actors and sub activities for a biopharma firm (B1). The clinical phase is

where the clinical trials are carried out and the product must pass through all the trials to finally get registered in the market (B1).

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

The interviewees from company 1 together provided answers to what the key actors and factors in the valley of death are for biopharma companies. An overview of these can be seen here in table 5-1, split over the six different categories as previously used in the literature review and the Vintura interviews. In each cell, one actor or factor is presented, with the source in brackets showing in which interview(s) it was mentioned. More specifically, if there is only one interviewee source presented for an actor or factor, it means that the other interviewee did not select this as a key actor or factor.

In the following paragraphs there will be an explanation of what actors and factors are related to the main goals, and if there also are additional actors and factors mentioned that could not be coupled to a goal.

Actors and factors for the goal 'develop the right product'

When an idea is developed further into a product, the factor cost-effectiveness of the technology should be considered, since it is important to be able to tell whether a product has the potential to be better than existing treatments in the market (B8). If a product is too expensive compared with the competition it is not feasible, even though it might be highly innovative and interesting (B1). Moreover, if the product will have any commercial issues, e.g. the medicine does not taste good or it gives a dry mouth as a side effect, it is important to tackle these in time. This is usually discovered during the clinical phase (B1), where a project manager with leadership skills is needed to oversee the whole product development process (B1). Having skills of self-awareness and self-criticism in the company can help to understand what technology has the real potential (B8). In order to know if the development is going in the right direction, it is smart to involve KOLs to get external advice (B8).

Actors and factors for the goal 'find sufficient funding'

The key factor in this activity is access to capital (B1, B8). It is important to have either a strong Chief Executive Officer (CEO) (B1) or someone else internally with good professionalism and business sense skills that can communicate with the investors (B8). The person talking with investors needs to be a good communicator in order to convince the investors that it is an interesting project to support (B8). The R&D activities require sufficient funding, however the Phase III studies in the clinical phase are by far the most expensive activities for a biopharma firm, which needs to be considered when trying to find capital (B1). Due to the resource-intensive clinical phase, another scenario is that a big pharma company acquires the biopharma firm. In that way, the big pharma company gets access to an innovative idea, and the biopharma firm gets support with capital and other resources (B1).

Table 5-1: Actors and factors from company 1

	(1) Technology	(2) Skills	(3) Resources	(4) Planning & process	(5) Market	(6) Regulations
Factors	Innovative idea [B8]	Leadership skills [B1]	Access to capital [B1, B8]	Access to patients [B1]	Network around the company [B8]	Regulations [B1, B8]
	Cost-effectiveness of technology [B1, B8]	Communication [B1, B8]	Human resources[B1, B8]	Intellectual Property set-up [B1, B8]		
	Commercial issues [B1]	Right skills & resources at right time [B8]	Information Technology [B1]	Realizing when patent should be filed [B8]		
		Professionalism & business sense [B8]		Manufacturing process [B8]		
		Relevant knowledge & innovative capabilities [B1, B8]				
		Relationship mgmt. [B1]				
		Self-awareness & self-criticism [B8]				
		Commitment [B8]				
Actors			Investors [B1, B8]		Patients [B1]	FDA [B1]
			Basic scientist [B8]		Hospitals [B1]	EMA [B1]
			Clinical scientist [B1]		Physicians [B1]	Competent Authorities [B1]
			Project manager [B1]		Key Opinion Leaders [B1, B8]	Central Ethics Committee [B1]
			Entrepreneur [B8]		Complementary technology providers [B1, B8]	
			Analytical arsenal (quality) [B8]		Big pharma firm [B1, B8]	
					Contract Research Organizations [B1]	

Actors and factors for the goal 'right skills and resources at right time'

The different activities and sub phases in the valley of death require the biopharma firm to have the right skills and resources at the right time. The entrepreneur can contribute in the process of finding talented candidates (B8). Complementary technology providers are crucial to bring in to compensate for the lack of a certain resource, e.g. for production support (B1), as well as a suitable partner for human resources (B8). The biopharma firm benefits from having a good network around the firm, e.g. to get advice or find a suitable partner, since usually a biopharma firm cannot perform all activities on its own within the valley of death (B8). A key activity in the valley of death is therefore to start building a network consisting of various expertise, skills and resources (B8).

Actors and factors for the goal 'make intellectual property set-up'

It is important that the biopharma firm realizes when a patent should be filed (B1, B8). If the product targets a rare disease, it might be possible to get additional protection due to the Orphan Drug Act (B8). When choosing a set-up, there has to be a balance between disclosing information and the risk of that the idea gets stolen (B1).

Actors and factors for the goal 'plan & execute clinical trials'

When designing the clinical trials, biopharma firms can reach out to Key Opinion Leaders and get advice on both the design and how to interpret the results from there (B1). The KOLs are experts with a scientific focus, and they are in many cases belonging to academia. The biopharma firm also needs scientific and regulatory advice from FDA and EMA continuously in the clinical phase, and especially just before starting Phase III: the most critical and expensive testing phase (B1). The authorities Competent Authorities (CA) and Central Ethics Committee (CEC) also needs to be communicated with to know what they look at e.g. from an ethical perspective (B1). During the execution of the clinical trials, a project manager is in the lead, and the biopharma firm needs to work with hospitals. That requires good relationships with physicians, who are the clinical investigators during the tests and provides getting access to patients. A biopharma firm can use a Contract Research Organization (CRO) to get operational support during the execution of the clinical trials, where the CRO is the local contact for the physician (B1).

Other important actors and factors

The interviews from company 1 also resulted in two additional factors that could not yet be related to one of the main goals described in these interviews. The first factor is 'commitment' because the firm needs to keep a forward-looking approach during the valley of death, and being committed towards a final goal can have a positive influence on traveling through the valley of death (B8). Another factor is 'IT solutions', since incorporating advanced IT solutions can really help the firm with its operations during the drug development process (B1).

Table 5-2: Author's interpretation of interconnections actors and factors in main goals from company 1

Main goal	Actors	Factors	Relation
1. Develop the right product	KOLs, project manager	Cost-effectiveness of technology, commercial issues, self-awareness & self-criticism, advice, leadership skills	A project manager with leadership skills is needed to oversee the process. KOLs can provide valuable advice to a biopharma firm about whether the product development is heading in the right direction.
2. Find sufficient funding	Investors, big pharma firm	Access to capital, professionalism & business sense, communication	Access to capital can come from investors, or if the biopharma firm gets acquired by a big pharma firm. When reaching out for capital, the skills 'professionalism & business sense' and 'communication' are critical to have.
3. Right skills & resources at right time	Entrepreneur, suitable partner	Complementary technology providers, network around company, human resources	An entrepreneur can contribute to find the right skills and resources. Suitable partner is providing access to human resources.
4. Make IP set-up	-	Realizing when patent should be filed	No interconnections explained.
5. Plan & execute clinical trials	KOLs FDA, EMA, project manager, hospitals, physicians, CRO	Advice, regulations, access to patients	KOLs can provide advice about the design and execution of clinical trials. The biopharma firm must follow regulations from FDA and EMA. A project manager is in charge and works with hospitals and physicians. The hospitals and physicians provide access to the right patients.
Other actors and factors mentioned in interviews in company 1	-	IT, commitment	No clear relation between these factors was described.

SQ3: *"How are the actors and factors in this phase interconnected?"*

During the interviews from company 1, the interviewees each created one picture of overviews of interconnections in the valley of death. These can be seen in figure 5-2 and 5-3. In table 5-2, an overview of the most important interconnections per goal can be seen. These relations were identified based on the information from the interviews in company 1, meaning that some of them were more implicitly explained and analyzed by the thesis author to be included in the table.

The first interview from company 1 (B1) described some interconnections between actors and factors with a focus on the clinical sub phase in the valley of death. These have already been discussed in table 5-2, but in figure 5-2 is the total visualization of the cards with actors and factors.

The second interview from company 1 (B8) resulted in an overview of interconnections focused on the discovery and R&D sub phase in the valley of death. Through this, the two pictures

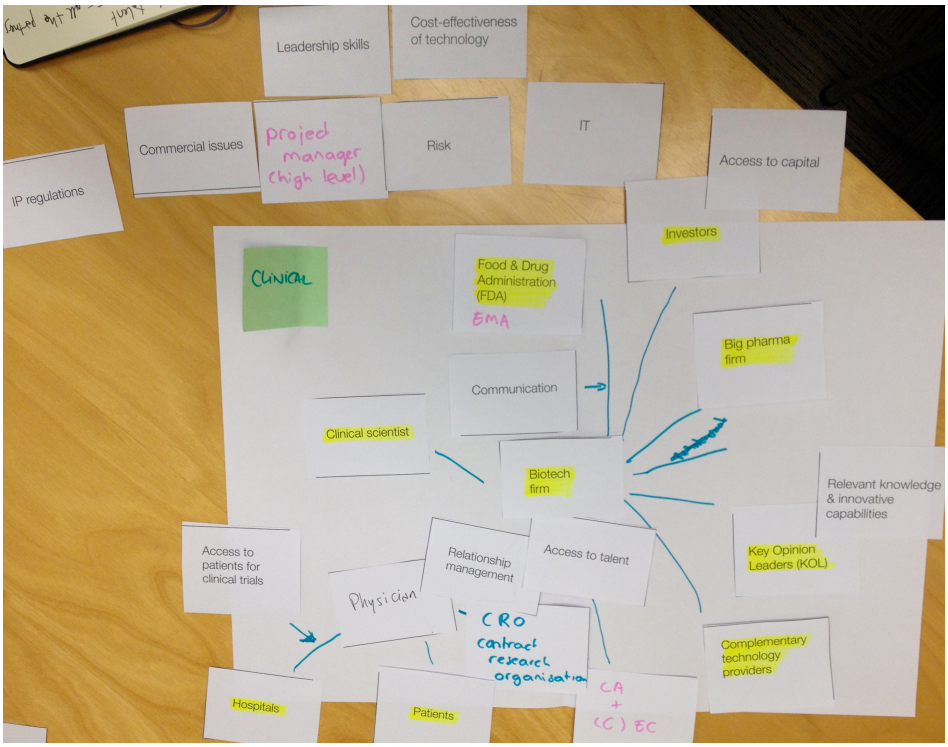

Figure 5-2: Overview of interconnections clinical phase (B1)

provide coverage of two sub phases in the valley of death. The overview of the actors and factors from interview B8 can be seen in figure 5-3.

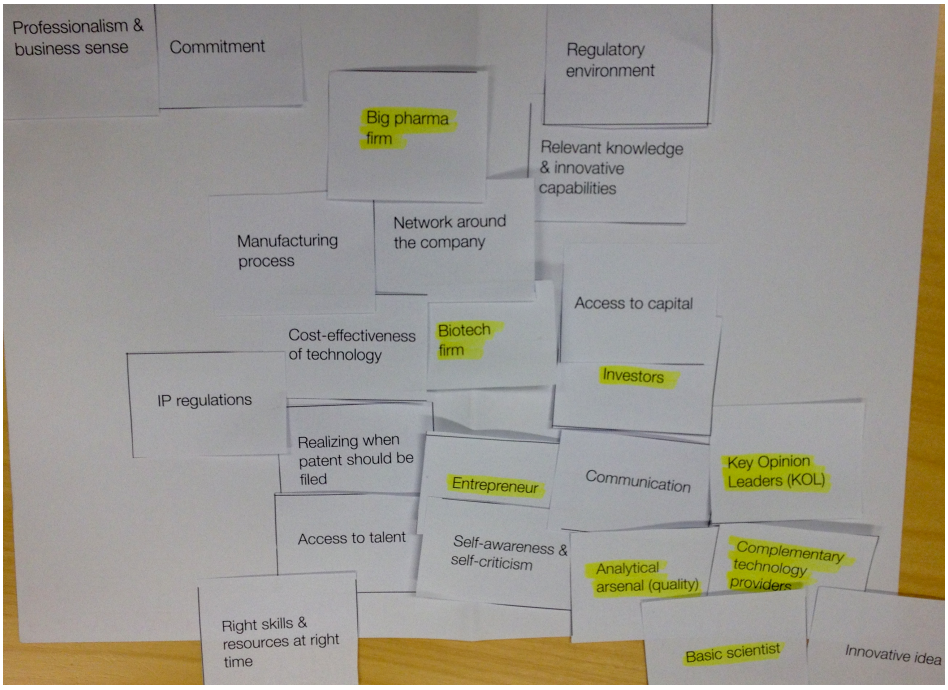

Figure 5-3: Overview of interconnections discovery & R&D (B8)

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

Due to a time constraint, this sub question regarding strategies was not explicitly discussed in interview B8. However, some remarks from the interviewee can still be interpreted as strategies and they will be included here. The majority of the strategies to survive the valley of death are therefore from interview B1, and they are related to some of the main goals.

Strategies targeting the goal 'develop the right product'

For the first goal 'develop the right product', the suggested strategy is to evaluate knowledge gained in clinical trials and tackle issues (B1). This is targeted towards dealing with potential commercial issues that can occur in the product development process.

Strategies targeting the goal 'find sufficient funding'

The second goal 'find sufficient funding', received the recommendation to have a strong person internally that can reach out to and communicate with investors (B1). Through this, the issue with potentially lacking professionalism and business sense skills can be dealt with.

Strategies targeting the goal 'right skills & resources at right time'

Following this, the third goal 'right skills & resources at right time' received two strategies, or two versions of a strategy to tackle slightly different issues within this goal. In order to deal with the blockage of having a sufficient network around the company, the suggested strategy is to make sure to have people internally that are able to build external contacts (B8). Another version of this strategy can target the need to have a project manager with communication skills by making sure to have persons internally with good communication skills (B8).

Strategies targeting the goal 'make intellectual property set-up'

The fourth goal 'make IP set-up' is targeted with two quite opposing strategies from company 1. The first strategy is to file patent early and then talk openly about the idea (B8), and the second one is to not use patents in order to keep trade secrets (B1). The second strategy means that no competitor is able to exactly copy the product and process after a patent expires (B1). These are both two different approaches on how to deal with the issue of timing of the patent filing.

Strategies targeting the goal 'plan & execute clinical trials'

Finally, the fifth goal 'plan and execute clinical trials' was approached by two different strategies. The first one is to know how the authorities evaluate the end-result and plan accordingly (B1), in order to deal with the barrier from policymakers and their regulations. Finally, the second suggested strategy is to communicate with CA and CEC to make sure to get authorization to start clinical trials (B1).

Strategies targeting other situations

One strategy was proposed that could not yet be coupled to one of the main goals from company 1. The suggested strategy is to involve KOLs to get advice on how to make a suitable design of trials (B1).

5-4 Company 2

This section consists of the same structure as for section 5-3, with one part describing the company and the interviewees, and the second presenting the interview results per sub question.

5-4-1 Description Company 2

The second company is another smaller public biopharma firm founded around 15 years ago, currently employing around 200 persons. The company focuses on the discovery and development of therapeutic antibodies. The company succeeded to get products to the market through partnerships, and has several other products in the pipeline from early discovery until clinical stage. The competitors of company 2 are basically all pharma and biopharma firms that are active in the field of antibody therapeutics, since it is quite a specialized field.

The two persons interviewed in company 2 have two different positions in the company, where interviewee "B5" is working within the research and development, and interviewee "B6" within pre-clinical operations (former employee). In interview B5, the discovery and R&D sub phase of the valley of death was discussed in detail since the interviewee is working with novel innovations and the building of new technologies in antibody biology and engineering. The interviewee has been employed in company 2 for a long time and therefore had a lot of experiences to share. The focus of the second interview, B6, was also on the discovery and R&D sub phase. The interviewee had a position working in the pre-clinical operations in company 2 for more than a decade, and could therefore explain the valley of death from a more operational perspective. In total, these two interviews provided a story about the early stages in the valley of death.

5-4-2 Results Company 2

The results from this company come from two interviews, which are B5 and B6.

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

Characteristics of the valley of death

The two interviewees from company 2 confirm the time frame of the valley of death to be between 10 and 15 years (B5, B6), which is in line with the previous research results in this

thesis. In order to get through the valley of death it is necessary for a biopharma firm to take calculated risk in order to create a new product. In general, this is the main difference compared with big pharma firms, who are more reluctant to take risks and therefore falls behind the biopharma firms on innovative capacity (B6).

Main goals in the valley of death

These two interviewees described a total of five different main goals that the companies should aim for in the valley of death. Some goals are the same as in company 1, and then only the differences or additions to those goals are described. Figure 5-4 shows an overview of all the five goals from the interviews in company 2.

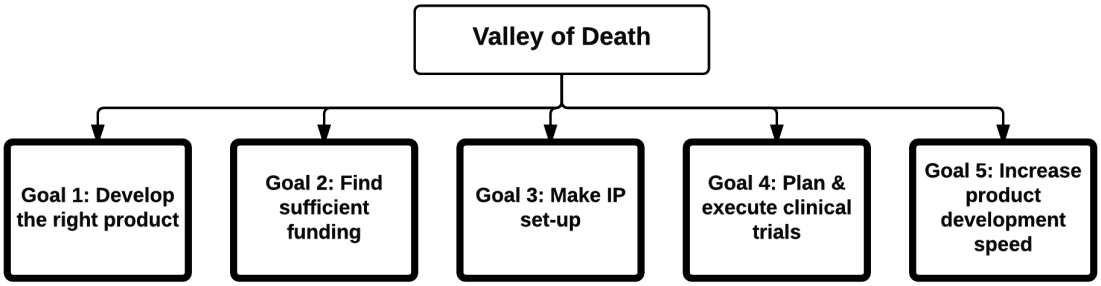

Figure 5-4: Overview of goals in the valley of death from company 2

The first goal from company 2 is to develop the right product. As also mentioned in company 1, it is important that the product has a higher potential than the competition and is interesting both from a scientific as well as from a patient perspective (B5). Moreover, the final drug needs to meet the safety and efficacy expectations (B5, B6), and the cost of the drug should be feasible both regarding the production and the price compared with existing treatments (B6). A biopharma firm usually has a resource-constraint, and therefore fewer candidate molecules to work on than a big pharma firm, and therefore it is key to focus the resources on creating a differentiated product with high quality (B5). The biopharma firm has to think about the future and the knowledge required developing a product that also fits to the needs of the patient, and can meet future trends such as personalized medicines (B5).

The second goal is also in alignment with the results from company 1, as both interviewees explained that access to capital is crucial before the biopharma makes its own money (B5, B6). There is in general a resource-constraint for a biopharma firm, meaning that choices need to be made on what to develop based on the knowledge and resources available (B5).

As described in company 1, one key goal in the valley of death is deciding about a suitable IP set-up (B5, B6). A biopharma firm needs to decide what information to share with the outside world (B6), and should make sure to have something innovative to patent in order to protect the idea (B5).

The fourth goal is about the planning and execution of clinical trials. This is important in order to create an overview of the whole development process (B6). During the execution it is relevant to bring in capacities of other partners since it is hard for a biopharma firm to do everything on its own (B6).

Finally, the fifth goal from company 2 is to increase product development speed. Being first to market with an innovative product is clearly an advantage, and therefore it is crucial to speed up the development. Ideally, all processes should be performed as fast as possible, although some steps are unfortunately hard to speed up and are still required for the development (B6).

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

An overview of the categorized actors and factors from the interviewees from company 2 can be found in table 5-3. As for company 1, the cells in the table show in brackets which interviewee(s) pointed the actors/factor out to be important in the valley of death. In the following paragraphs there are a descriptions of what actors and factors belong to the main goals identified in this thesis. Some actors and factors that cannot be related to a goal are mentioned separately.

Actors and factors for the goal 'develop the right product'

As mentioned in company 1, the cost-effectiveness of the technology is a critical factor to consider in the development of the right product (B6). Additionally, the cost of goods also needs to be manageable, (B6), and the biopharma firm needs advice to understand where the unmet medical need is, which can be provided by e.g. insight generators with various expertise and functions (B6). Furthermore, the FDA and EMA can be involved to check whether the plans are realistic, already at an early stage of product development (B6). In order to develop the right product it is crucial that the technology has sufficient safety (B5, B6), and that potential commercial issues get early attention (B6). Due to stricter regulations from policymakers, it is necessary for a biopharma firm to have a good market understanding (B5, B6), and also include the added value for the patients as an outcome (B5). Added to this, a project manager with leadership skills (B6) is in charge of the operational activities to create an innovative product (B5). Self-awareness & self-criticism is required to be able to take difficult decisions about which product to develop further (B5, B6).

Actors and factors for the goal 'find sufficient funding'

As similarly described in company 1, access to capital is a key factor in this activity, where external investors usually are needed for a biopharma firm (B5, B6). Capital can also be accessed from big pharma firms (B5), either through a licensing agreement or acquisition, which also was mentioned in company 1. A good network around the company can help in the process of finding external actors that are interested in investing (B5, B6).

Actors and factors for the goal 'make intellectual property set-up'

As described in company 1, realizing when a patent should be filed is very important (B6), but according to one interviewee in company 2 it is more important that the firm has an innovative idea that is patentable (B5). It is crucial to have good market understanding to know how to make a suitable IP set-up (B5). It is also good to get advice about IP regulations in order

Table 5-3: Actors and factors from company 2

	(1) Technology	(2) Skills	(3) Resources	(4) Planning & process	(5) Market	(6) Regulations
Factors	Innovative idea [B5, B6]	Leadership skills [B5, B6]	Access to capital [B5, B6]	Design of clinical trials [B6]	Network around the company [B5, B6]	Regulations [B6]
	Cost-effectiveness of technology [B6]	Communication [B6]	Human resources [B5, B6]	Intellectual Property set-up [B5, B6]		
	Commercial issues [B6]	Right skills & resources at right time [B6]	Technological resources [B6]]	Realizing when patent should be filed [B5, B6]		
	Cost of goods [B6]	Professionalism & business sense [B6]		Manufacturing process [B6]		
	Product safety [B5]	Relevant knowledge & innovative capabilities [B5, B6]		Suitable organizational structure [B5]		
		Relationship mgmt. [B5, B6]				
		Self-awareness & self-criticism [B5, B6]				
		Commitment [B5, B6]				
Actors			Investors [B5, B6]		KOLs [B5, B6]	FDA [B6]
			Basic scientist [B5, B6]		Complementary technology providers [B5, B6]	EMA [B6]
			Clinical scientist [B6]		Big pharma firm [B5]	
			Project manager [B5, B6]		CROs [B5, B6]	
			Entrepreneur [B5, B6]		Contract Manufacturing Organizations [B5, B6]	
			Analytical arsenal (quality) [B6]		Academia [B5, B6]	

to not make any beginners mistakes (B6). Working with big pharma firm requires protected ideas in order to ensure getting capital from them, which is why a potential collaboration should be considered when thinking of IP set-up (B5).

Actors and factors for the goal 'plan & execute clinical trials'

Suitable partners such as Contract Manufacturing Organizations (CMO), CROs and clinician-scientists can provide support for manufacturing the drug, managing the clinical trials, and give valuable insights on clinical applications respectively (B5, B6). Overall, a project manager is needed to bring everything together during the clinical phase (B6).

Actors and factors for the goal 'increase product development speed'

In order to get through the valley of death as fast as possible, having commitment can facilitate a biopharma to do so (B6). The regulatory environment is something that a biopharma really needs to be aware of in order to carry out the product development faster (B6). The clinical phase is very resources intensive, which means it is critical to work with a suitable partner to find the right resources, e.g. complementary technology providers to get technological resources (B6). One key factor in speeding up in the valley of death is to have a good design of clinical trials (B6).

Other important actors and factors

Company 2 also generated two additional actors and factors that are important in the valley of death. The first one is an entrepreneur with relationship management skills, which is important for a biopharma to have to establish good contacts outside of the firm (B6). The second one is finding a suitable partner in order to access human resources (B6).

SQ3: *"How are the actors and factors in this phase interconnected?"*

In table 5-4 is an overview of the mentioned relations between actors and factors from the interviewees in company 2. They are split up per main goal, and the relationships between them are described. The last row is summarizing the actors and factors that do not belong to a main goal at the moment. As mentioned for the literature, Vintura interviews, and company 1, this table with interconnections was made based on the information from the interviewees in company 2, where some things were mentioned more implicitly and some more explicitly.

Table 5-4: Author's interpretation of interconnections actors and factors in main goals from company 2

Main goal	Actors	Factors	Relation
1. Develop the right product	Insight generators, project manager, FDA, EMA, policymakers	Cost of goods, cost-effectiveness of technology, commercial issues, technology safety, self-awareness & self-criticism, advice, leadership skills, market understanding, regulations	A project manager with leadership skills is needed to oversee the process. The firm can get valuable advice from insight generators about whether the product development is heading in the right direction. FDA and EMA can also give advice on this. Policymakers set the regulations that a biopharma firm must follow.
2. Find sufficient funding	Investors, big pharma firm	Access to capital, network around company	Investors, or if the biopharma firm gets acquired by a big pharma firm can generate access to capital for a biopharma firm.
3. Make IP set-up	-	Advice, IP regulations, market understanding	Advice about IP regulations can enhance the chances of making a good IP set-up.
4. Plan & execute clinical trials	CMO, CRO, clinician-scientists, project manager	-	CMOs, CROs and clinician-scientists can all support in the planning and execution of the clinical trials.
5. Increase product development speed	Suitable partner, complementary technology providers	Commitment, regulations, technological resources, design of clinical trials	A suitable partner can provide resources needed, e.g. complementary technology providers can offer technological resources.
Other actors and factors mentioned in interviews in company 2	Entrepreneur, suitable partner	Relationship mgmt. skills, human resources	An entrepreneur with relationship mgmt. skills is beneficial for the firm when reaching out to external stakeholders. A suitable partner can bring in human resources.

The interviewees from company 2 created one picture each of overviews of interconnections in the valley of death, both focused in the early valley of death. These can be seen in figure 5-5 and 5-6. The results include how actors and factors are interconnected, and how they link to the defined main goals. These interconnections are described in words in table 5-4.

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

The interviews from company 2 provided strategy suggestion for the five main goals as identified in these interviews, and some additional strategies.

Strategies targeting the goal 'develop the right product'

The first goal 'develop the right product', received five strategy suggestions. The first two are make sufficient testing of the product to ensure safety (B5), and take all signals seriously that the drug is not safe (B5). These are both directed to ensure product safety when developing

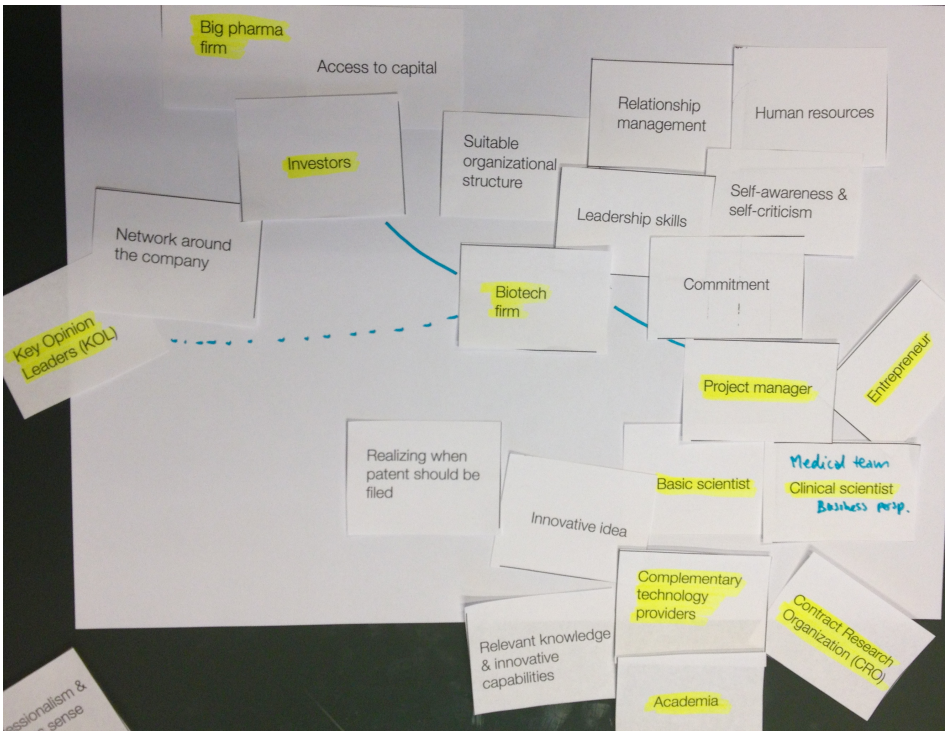

Figure 5-5: Overview of interconnections in the discovery and R&D sub phase (B5)

Figure 5-6: Overview of interconnections in the discovery and pre-clinical sub phases (B6)

the right product further. Following this, the next strategy is to be forward-looking in the approach (B5, B6). Another strategy is to have insights in the competitive landscape (B6). Both of these strategies are targeting getting an improved market understanding. Finally, the last strategy is adapt the product to fit with current regulations (B6), which is related to the issue about strict regulations for the drug development.

Strategies targeting the goal 'find sufficient funding'

The second goal 'find sufficient funding', is targeted with a total of four strategies. The first one is to seek investors that bring in knowledge and network (B6), when finding a suitable investor. The second strategy can be used towards any external actor that the biopharma firm wants to access capital from: make sure to have a good and scientific sound story (B6). Having a convincing story increases the chances of finding interested external parties that want to invest. The next strategy is license out the product to big pharma (B5), which is one way to get capital from a big pharma firm. Finally, the fourth strategy is make sure the idea is protected with a good IP set-up (B5), which is important for a big pharma firm to be interested in investing.

Strategies targeting the goal 'make intellectual property set-up'

For the third goal 'make IP set-up', there is one strategy proposed: file patent early and then go and talk openly about the idea (B5). Then the idea is protected and the company can get a lot of input from the outside world by talking about the idea and not risking it to be stolen.

Strategies targeting the goal 'plan & execute clinical trials'

For the goal 'plan & execute clinical trials' there is one strategy proposed, which is to use capabilities of partners (e.g. CRO) to manage the execution of clinical trials (B6).

Strategies targeting the goal 'increase product development speed'

Finally, for the goal 'increase product development speed', one strategy is suggested: find a partner that covers the lack of expertise needed (B5, B6). By doing so, it can save a lot of valuable time for the biopharma firm, since a partner might already have expertise in an area relevant for the drug development.

Strategies targeting other situations

There was one additional strategy mentioned that could not yet be linked to a main goal in this case: find a partner that covers the lack of expertise needed (B5, B6).

5-5 Company 3

This section presents the results from company 3 per sub question, where the information comes from interview B3 and from B4.

5-5-1 Description Company 3

The third company is a mid-size multi-national firm, producing both classical pharmaceutical products as well as biopharmaceuticals. This company is headquartered in the EU and has over 100 products in the market.

The two persons interviewed in company 3 have two different positions in the company, where the interviewee "B3" has a high position in the biotech research area, and interviewee "B4" is working with the global lead for evidence generation towards payers and other healthcare decision makers. The interviewee in interview B3 was involved in the early phase of the biotech science part of the company, and therefore has a lot of experiences from the biopharma activities within the company. During the interview, the focus of the interconnections between actors and factors was from the clinical sub phase in the valley of death. In the second interview, B4, the interviewee?s team focuses on late-phase clinical development through to and beyond commercialization. Therefore the focuses of this interview during the interactive session about interconnections were centered on the clinical and launch preparation sub phases of the valley of death.

5-5-2 Results Company 3

The results from this company come from two interviews, which are B3 and B4.

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

Characteristics in the valley of death

The time frame of the valley of death is once again confirmed to be between 10 to 15 years for biopharma firms (B3, B4). One interviewee also estimated the length of the various sub phases in the valley of death to be the following: discovery and pre-clinical testing 3-5 years, clinical trials and launch preparation 7-10 years, filing and registration 6 months-1 year, and finally the authorities approval about 1 year (B3).

Main goals in the valley of death

The two interviewees brought up in total five different main goals that take place in the valley of death. All of these were also brought up in company 1 and some in company 2, so here only the differences or additions to those goals will be described. Figure 5-7 presents a visualization of these goals.

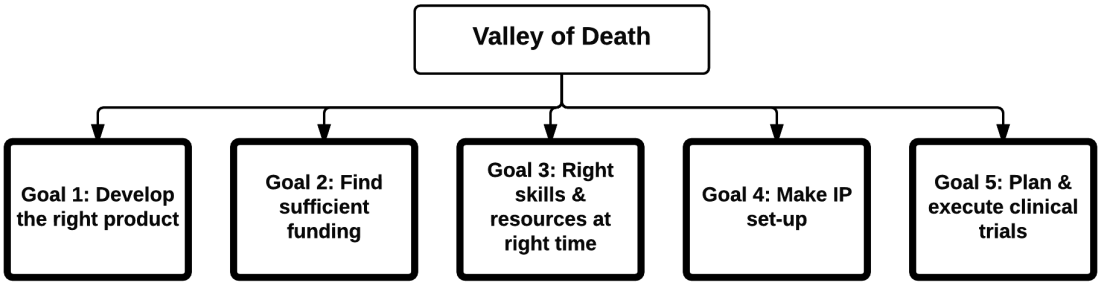

Figure 5-7: Overview of goals in the valley of death from company 3

In line with company 1 and 2, the first goal, develop the right product, was described in company 3 as being important. The biopharma firm needs to compare its idea with what the competition is doing, especially to make sure the product is clinically differentiated and targets an unmet medical need (B4).

As mentioned in both company 1 and 2, a biopharma firm needs to find sufficient funding to keep developing (B3). A larger biopharma firm might be able to use internal capital from the budget, but must divide the funds over several research projects or apply for state funding in collaborative projects (B3).

The third goal of having the right skills and resources at the right time is important during the whole valley of death (B3), which also was mentioned in company 1. Usually for a biopharma firm this involves finding external partners to work with (B3).

As described in company 1 and 2, making an IP set-up is important to protect the idea towards competitors (B3). Added to this, if a biopharma firm works in an idea-sharing setting, there is a need for IP contracts between the partners (B3).

Finally, the fifth goal is to plan and execute clinical trials. The clinical phase is in general the most critical one where a biopharma firm either can make it or break it (B3). There is interaction between the biopharma firm and the authorities during the clinical phase for the firm to get scientific advice and permission to do the trials (B4).

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

Table 5-5 shows an overview of the actors and factors identified from company 3, divided over the six categories as used for the previous company interviews. As mentioned for company 1 and 2, the interviewee sources are presented for each actor and factor in the cells in the table. This means that if an interviewee source is not present for a specific actor/factor, this was not considered an important actor/factor by that interviewee. The following paragraphs contain descriptions of how the actors and factors are connected to the main goals from company 3.

Table 5-5: Actors and factors from company 3

	(1) Technology	(2) Skills	(3) Resources	(4) Planning & process	(5) Market	(6) Regulations
Factors	Innovative idea [B4]	Leadership skills [B4]	Access to capital [B3]	Design of clinical trials [B3, B4]	Market understanding [B4]	Regulations [B3, B4]
	Cost-effectiveness of technology [B4]	Communication [B3]	Human resources[B3, B4]	Access to patients [B3, B4]	Network around the company [B3]	
	Commercial issues [B4]	Right skills & resources at right time [B3]	Technological resources [B3]	Intellectual Property set-up [B3]	Market access criteria [B4]	
	Cost of goods [B3]	Relevant knowledge & innovative capabilities [B3, B4]	Support resources [B3]	Realizing when patent should be filed [B3]		
	Product safety [B4]	Relationship mgmt. [B4]	Information Technology [B3]	Manufacturing process [B3]		
		Relationship mgmt. [B1]				
	Clinical & market supply [B3]	Commitment [B3]		Suitable organizational structure [B3]		
Actors			Investors [B3]		KOLs [B3, B4]	FDA [B3, B4]
			Clinical scientist [B3, B4]		Big pharma firm [B3]	EMA [B3, B4]
			Clinician-scientist [B3]		CROs [B3, B4]	Policymakers [B4]
			Project manager [B3, B4]		CMOs [B3]	
			Suitable partner [B4]		Academia [3]	
			Analytical arsenal (quality) [B3]		HTA agencies [B4]	
			Regulatory affairs [B3]		Physicians [B3, B4]	
			Insight generators [B4]		Patients [B3, B4]	
					Hospitals [B3, B4]	

Actors and factors for the goal 'develop the right product'

When developing a product, the cost of goods can positively influence the choice of going in a certain direction, since a lot of capital can be saved here (B3). By reaching out and trying to understand the patient needs, a biopharma firm can get a better idea of what product they should develop (B3). In line with company 1 and 2, the cost-effectiveness and product safety of the technology is also pointed out as key factors in this goal (B4). Moreover, the biopharma firm needs to know the market access criteria, where HTA agencies play a role in evaluating the final product (B4). Leadership skills are needed internally in the biopharma firm in order to make difficult decisions to stop developing a certain product (B4), which are described as self-awareness & self-criticism in company 2. Policymakers also play a role in what products are beneficial to make, since they can allocate spending to e.g. focus on one type of disease prevention (B4).

Actors and factors for the goal 'find sufficient funding'

In company 3, as in company 1 and 2, the factor access to capital was brought up as the crucial factor to find sufficient funding, and external investors as a key actor in this activity (B3).

Actors and factors for the goal 'right skills & resources at right time'

The biopharma firm needs access to different skills at different points in time, meaning that they usually need to collaborate with partners to find missing skills or human resources (B4). This is e.g. academia to get ideas, hospitals and physicians to carry out clinical trials and get access to patients, and a project manager should oversee the whole process to reach out to partners (B3). Support resources can benefit the biopharma firm in the development process (B3).

Actors and factors for the goal 'make intellectual property set-up'

It is important that the biopharma firm realizes when patent should be filed, which preferably should be done before the clinical phase (B3).

Actors and factors for the goal 'plan and execute clinical trials'

A project manager is overseeing the clinical work (B4). Initially, a biopharma firm needs authorization from FDA or EMA to start clinical trials (B3), and advice from KOLs on the plan can have a positive influence (B4), as also described in company 1 and 2. The policymakers are setting the overall stage of what is beneficial to produce for the market (B4). Using CROs for the operations of the trials, and CMOs for the manufacturing process can help the biopharma firm in this phase (B3). The biopharma firm should also understand the market access criteria from the HTA agencies in order to make a good design of the clinical trials (B4). The design of clinical trials is a key factor, which if done wrong can lead to failed clinical trials (B3). The clinical scientists are critical for doing a lot of the operations within the firm (B3, B4). For the rest, hospitals and physicians provide access to patients, which are needed for the testing (B3).

Other important actors and factors

One interviewee included clinical & market supply as an important factor during the valley of death (B3). This means having sufficient supply of the drug for carrying out clinical tests but also to launch the drug in the market, but is an often neglected, or taken for granted, aspect by the firm (B3).

SQ3: *"How are the actors and factors in this phase interconnected?"*

The overview of the interconnections between actors and factors in the valley of death can be seen in table 5-6. This table was constructed in the same way as for previous company cases, where the information from the interviews in company 3 was interpreted to create the table. The following paragraphs contain presentations of the two visualizations created in company 3.

Table 5-6: Author's interpretation of interconnections actors and factors in main goals from company 3

Main goal	Actors	Factors	Relation
1. Develop the right product	Patients, project manager, HTA agencies, policymakers	Cost-effectiveness of technology, technology safety, cost of goods, advice, leadership skills, regulations, market access criteria	Patients can provide an advisory perspective on what product a biopharma should develop. The HTA agencies decide on the market access criteria, and policymakers about relevant regulations. A project manager with leadership skills can oversee the process and make difficult decisions.
2. Find sufficient funding	Investors	Access to capital	Access to capital can come from external investors.
3. Right skills & resources at right time	Suitable partner, project manager	Human resources, support resources	Suitable partner is providing access to human resources.
4. Make IP set-up	-	Realizing when patent should be filed	No interconnections explained.
5. Plan & execute clinical trials	KOLs FDA, EMA, project manager, clinical scientists, hospitals, physicians, patients CRO, CMO, HTA agencies, policymakers	Advice, regulations, access to patients, manufacturing process, market access criteria, design of clinical trials	Policymakers set the stage with the regulations, and FDA and EMA gives a biopharma firm authorization to start clinical trials. KOLs can give advice on the planning and execution of the trials, and CMOs and CROs can support with e.g. manufacturing process. The project manager needs to work with hospitals and physicians to get access to patients.
Other actors and factors mentioned in interviews in company 3	-	Clinical and market supply	-

From company 3 the two interviewees both created one picture each showing interconnections of actors and factors. The first interview focused on the clinical sub phase (B3) while the second one had the clinical and the launch preparation sub phases in the valley of death included. The respective picture from each interview can be seen in figure 5-8 and 5-9, where the interconnections are described in words in table 5-6.

Figure 5-8: Overview of interconnections in clinical sub phase (B3)

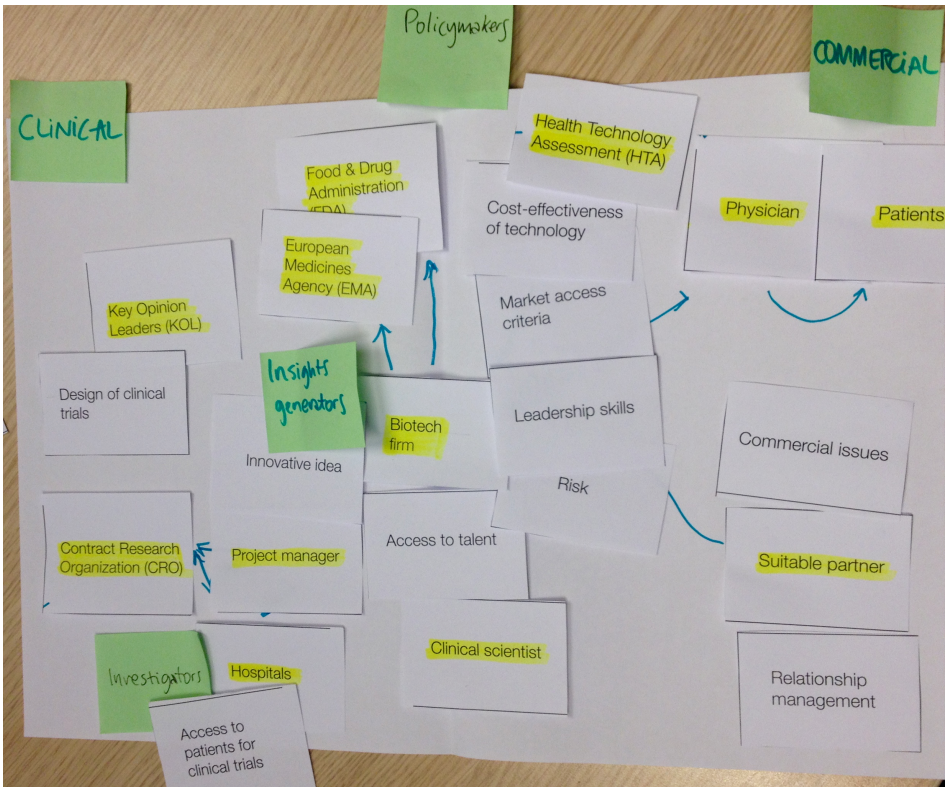

Figure 5-9: Overview of interconnections in clinical and launch preparation sub phases (B4)

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

The interviewees from company 3 provided strategies towards two of the main goals according to their view on the valley of death. Moreover, a few additional strategies were identified that cannot be linked to a main goal from company 3.

Strategies targeting the goal 'develop the right product'

The first goal 'develop the right product', is targeted with seven different strategies. The first two are directed towards the technology: make sure the product is clinically differentiated (B4) and take all signals seriously that the drug is not safe (B4). The third strategy is to try to predict future technology and patient behavior and needs (B3), which is suggested in order to deal with potential commercial issues that could occur with the product. This is of course difficult to do, but can be tackled with e.g. extensive market research and keeping track of trends in the industry. The following two strategies are proposed to get a better market understanding: understand the patient needs to see where to add value (B4), and have insights in the competitive landscape (B4). In order to tackle the problem with lack of self-awareness and self-criticism, the strategy be forward-looking in the approach (B3) was suggested. Finally, the last strategy is make sure to have a good project manager in charge of the product development (B4).

Strategies targeting the goal 'plan & execute clinical trials'

The fifth goal 'plan & execute clinical trials', received four strategy suggestions. The first one is make sure to have a good project manager in charge of the clinical trials (B4), which is almost the same as the last strategy mentioned in the first goal, with the difference that this is a focus on the clinical phase. Secondly, the next strategy is find the right hospital and physician to work with in order to get access to patients for clinical trials (B3). The third strategy is make sure to have clinical scientists who can execute the trials (B4). Finally, the fourth strategy is involve physicians to get the care perspective on how patients are treated (B4).

For the other three goals; 'find sufficient funding', 'right skills & resources at right time', and 'make IP set-up' there were no strategies suggested from company 3.

Strategies targeting other situations

In addition to the strategies for the main goals, there were four additional strategies suggested from company 3. The first one is 'make sure to have sufficient supply of the drug, both for clinical trials and for the market launch' (B3). The next strategy is 'involve KOLs to get advice on how to make a suitable design of clinical trials' (B4), which means that input from KOLs could result in a better design. The third strategy is 'use adaptive clinical trials' (B3), which is a way to speed up the trials and do several steps in parallel. Finally, the last strategy is 'lower the investment per treatment in order to test more' (B3). This is quite hard for a biopharma firm to do, but it would be ideal if possible since then there are many more candidates that potentially could make it to the market.

5-6 Company 4

This section presents the results from company 4 per sub question, where it is marked what information comes from interview B2 and from B7.

5-6-1 Description Company 4

The fourth and final company is the biotechnology business unit of a large global pharmaceutical firm. The business unit previously operated as a standalone company prior to its acquisition by the larger firm.

The two persons interviewed in company 4 have two different positions in the company, where interviewee "B2" is currently having a high position within the business/disease management development area and was previously in R&D. Interviewee "B7" is working in the management of clinical research and development. The first interview was focused on first discussing the valley of death in general, and then resulted in the creation of two pictures with overviews of interconnections. One was from the discovery and R&D sub phase, and one from the clinical sub phase in the valley of death. The interviewee has experiences from both sub phases, which provided an understanding of the majority of the valley of death. The second interview was carried out by phone, since the interviewee was abroad at that time. Due to this, the

results are a bit more limited, and also did not result in a picture with interconnections. This interviewee has a background as medical doctor and provided some general remarks about the valley of death, and some strategies that can be used in this phase.

5-6-2 Results Company 4

The results from this company come from two interviews, which are B2 and B7.

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

Characteristics of the valley of death

The valley of death is also in this last biopharma company confirmed to last around 10 years (B2). It is a strictly regulated and sensitive phase for biopharma firms, with uncertainties regarding the outcomes of the product. The clinical phase is incredibly difficult and the companies often underestimate how much more resource-intensive this is compared with doing discovery and R&D (B2). There are many ideas that do not make it through the whole valley of death, from an estimated 1000 ideas only 1-3 will make it into becoming a final product (B2).

Main goals in the valley of death

There were six different main goals described in these company interviews. In figure 5-10 is an overview of these, and then each goal will be further elaborated upon.

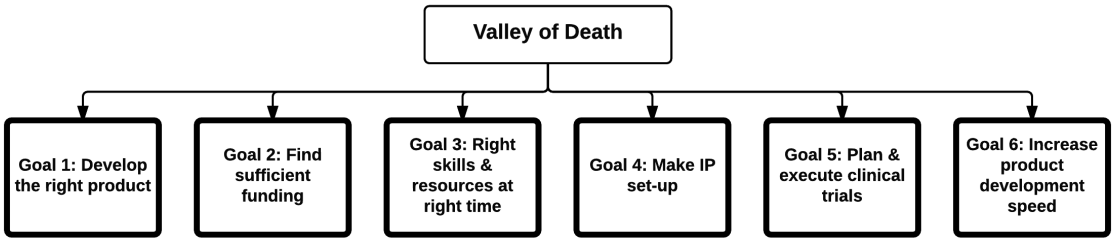

Figure 5-10: Overview of goals in the valley of death from company 4

The first goal is to develop the right product, which is about having a good scientific understanding of the product in order to create a solid proof-of-concept (B7). A biopharma firm should also look at disease from a business perspective to evaluate its future potential in the market (B2). As mentioned in company 1, potential commercial issues with the product will be discovered already in the clinical phase and should be dealt with in time (B2). Commercial issues include making sure the label claim is feasible, or understanding the complexity of the pharmacokinetic profile (B2).

Secondly, a biopharma needs capital and the need will exponentially grow the closer the clinical phase gets (B2). As mentioned in all previous company interviews, it might be necessary for the biopharma to find external capital to cover for this need (B2).

The third goal, right skills & resources at right time, is important for biopharma firms in the valley of death (B2), which also was described in company 1 and 3 above. Especially during the clinical phase the biopharma firm needs many different types of resources, which might mean that they have to look externally to find complementary skills (B2).

The fourth goal is to make IP set-up. The pharmaceutical industry is focused on having patent protection on products, and that somehow is valid for biopharma as well (2). However, sometimes a biopharma product is not patentable, by law (B2), but if the product is complex to make it also creates a kind of hurdle to replicate it (B7). A large part of the value of a biopharma firm lies in its intellectual property and talent (B7). If some information regarding the product has been presented in the public, it will be harder to file a patent, so the firm should consider this at an early stage (B2).

Following this, the fifth goal is to plan and execute clinical trials. As described in company 1 and 2, a biopharma firms needs to make a good design of the clinical trials, and work with partners to be able to manage the execution of the trials (B2). The clinical phase is where a company can make it or breaks it (B2), which was also mentioned in company 3.

Finally, the last goal is increase product development speed. A biopharma firm should aim for shortening the development time of a product to get it as fast as possible to the market (B2).

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

Table 5-7 provides the overview of the actors and factors defined by the interviewees in company 4, split over the previously used categories. In the same way as for the three previous companies, table 5-7 shows per cell what interviewee mentioned each actor/factor as important for biopharma firms in the valley of death. Following this is a description of actors and factors related to the main goals.

Actors and factors for the goal 'develop the right product'

In order to develop the right product, it should have some business attraction to be promising (B2). Having a large home market is not required, but it can provide an advantage to companies (B2). It can be good for a biopharma firm to reach out to Patient Advocacy Groups in order to get advice on the patient perspective on a disease (B2). The company must also understand the product well from a scientific point of view to make sure the product has the right properties, which in this case requires actors such as basic scientists (B7). Another key factor is to understand what the commercial issues are with a product, and the project manager should deal with communicating these issues to other actors in the company (B2).

Actors and factors for the goal 'find sufficient funding'

As mentioned in all previous company interviews, the key factor here is access to capital, and for smaller firms it is common to reach out to external investors to raise funding (B2). This

Table 5-7: Actors and factors from company 4

	(1) Technology	(2) Skills	(3) Resources	(4) Planning & process	(5) Market	(6) Regulations
Factors	Innovative idea [B2, B7]	Leadership skills [B2]	Access to capital [B2]	Design of clinical trials [B2]	Market access criteria [B2]	Regulations [B2]
	Commercial issues [B2]	Communication [B2]	Human resources[B2, B7]	Access to patients [B2, B7]	Large home market [B2]	
	Business attraction for product [B2]	Right skills & resources at right time [B2]	Information Technology [B2]	Intellectual Property set-up [B2, B7]		
		Relevant knowledge & innovative capabilities [B2, B7]		Realizing when patent should be filed [B2]		
		Relationship mgmt. [B2]				
		Self-awareness & self-criticism [B2]				
		Professionalism & business sense [B2]				
Actors			Investors [B2]		KOLs [B2]	FDA [B2]
			Basic scientist [B2]		CROs [B2]	EMA [B2]
			Clinical scientist [B2]		Physicians [B2]	Policymakers [B4]
			Clinician-scientist [B2]		Patients [B2]	
			Project manager [B2]		Hospitals [B2]	
			Suitable partner [B2, B7]		Academia [B2, B7]	
			Entrepreneur [B2]		HTA agencies [B2]	
					Competent Authorities (CA) [B2]	
					Central Ethics Committee (CEC) [B2]	
					Patient Advocacy Groups [B2]	

requires having skills of professionalism and business sense within the company, in order to know how to deal with external stakeholders (B2).

Actors and factors for the goal 'right skills & resources at right time'

The need of human resources is continuous for companies during the valley of death (B2, B7). During the clinical phase, a biopharma firm needs to make sure to have the right skills and resources at the right time, meaning the firm needs to use professionalism and business sense and good communication to achieve this (B2). The biopharma firm benefits from having suitable partners during the valley of death (B7), meaning that they need to focus on building a network around the company. The firm needs relationship management skills in order to create and maintain external relations (B2).

Actors and factors for the goal 'make intellectual property set-up'

The project manager and internal regulatory affairs should together realize when a patent should be filed (B2).

Actors and factors for the goal 'plan & execute clinical trials'

As described in company 1 and 2, the design of clinical trials is a key factor for this activity (B2). Many actors are involved in this phase, such as hospitals, physicians, patients, Patient Advocacy Groups, KOLs, CRO, HTA agencies, and an internal project manager that oversees the process (B2). It is crucial that the firm can find suitable partners to work with in order to get through the phase (B7). The Competent Authorities comes up with guidelines for clinical trials development that a biopharma firm should follow, and the CA together with FDA, EMA and the Central Ethics Committee give approval to a biopharma firm to get started with the clinical trials (B2).

Actors and factors for the goal 'increase product development speed'

There are two key factors that positively influence the speed of product development: a good design of clinical trials and good IT solutions within the company (B2). If a biopharma firm works with experienced people or outsources activities to a suitable partner such as a CRO, it can also increase the product development speed (B2). It is important that the biopharma firm considers the current regulations and adapts to them, in order to increase speed (B2).

SQ3: *"How are the actors and factors in this phase interconnected?"*

Table 5-8 shows an overview of actors and factors per goal, with the relevant relations described in the last column. These relations were found based on an interpretation of the interview results from company 4. The table shows an overview of these interconnections, and in figure 5-11 and 5-12 are the visualizations of the interconnections from the interviews.

Table 5-8: Author's interpretation of interconnections actors and factors in main goals from company 4

Main goal	Actors	Factors	Relation
1. Develop the right product	Patient Advocacy Groups, project manager	Business attraction for product, advice, commercial issues	Patient Advocacy Groups can provide an advisory perspective on what product a biopharma should develop.. A project manager should understand what potential commercial issues with the product can be.
2. Find sufficient funding	Investors	Access to capital, professionalism & business sense	Access to capital can come from external investors, and the biopharma firm needs to have professionalism & business sense when reaching out to investors.
3. Right skills & resources at right time	Suitable partner, project manager	Human resources, professionalism, communication, network around company, relationship mgmt. skills	Suitable partner is providing access to human resources. By using skills such as communication and relationship mgmt., a biopharma firm can start building a network around the company.
4. Make IP set-up	Project manager, regulatory affairs	Realizing when patent should be filed	A project manager together with regulatory affairs should realize when a patent should be filed.
5. Plan & execute clinical trials	KOLs FDA, EMA, project manager, hospitals, physicians, patients, Patient Advocacy Groups, CRO, HTA agencies, suitable partner	Advice, regulations, access to patients, design of clinical trials	FDA, EMA, CA and CEC give a biopharma firm authorization to start clinical trials. The project manager needs to work with hospitals and physicians to get access to patients. A suitable partner can provide resources and skills needed in the valley of death.
6. Increase product development speed	Suitable partner	IT, regulations, design of clinical trials	No interconnections described between these actors and factors

In figure 5-11 and 5-12, the overview pictures of the interconnections as described in the interviews are displayed. The first picture is focused on the discovery and R&D sub phase, while the second one is about the clinical sub phase in the valley of death.

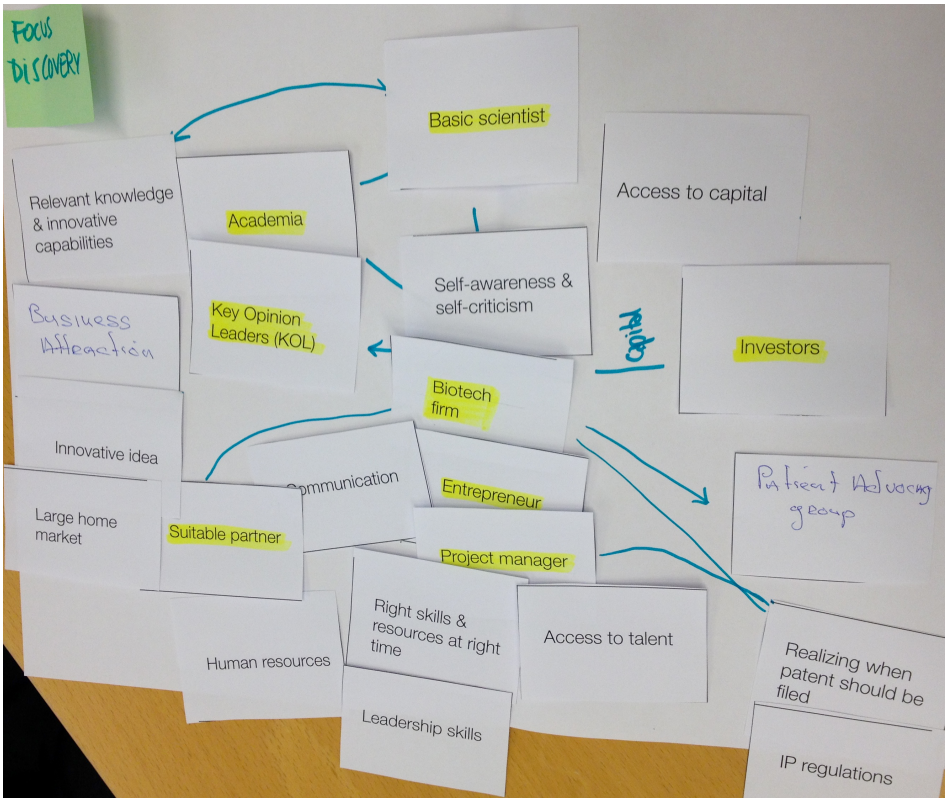

Figure 5-11: Overview of interconnections in discovery and R&D sub phase (B2)

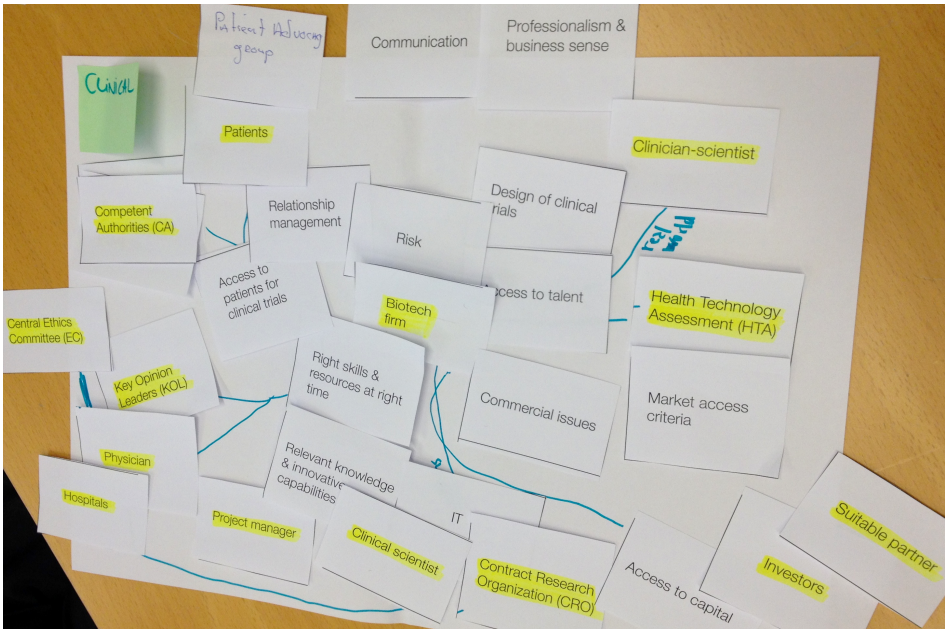

Figure 5-12: Overview of interconnections in clinical sub phase (B2)

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

From the interviews in company 4 there were strategies proposed for all the six goals identified from these interviews.

Strategies targeting the goal 'develop the right product'

For the first goal 'develop the right product', there is one strategy suggested: evaluate knowledge gained in clinical trials and tackle issues (B2). More specifically, this is referring to dealing with commercial issues for the product, e.g. an odd taste of the medicine, or the formulation in which the medicine will be delivered, e.g. injection or orally.

Strategies targeting the goal 'find sufficient funding'

The second goal 'find sufficient funding', is targeted with two strategies: (1) make sure to have a good and scientific sound story (B2), and (2) go public with the shares of the firm to gain capital (B2). These can be used when dealing with any external actor that could invest money into the firm.

Strategies targeting the goal 'right skills & resources at the right time'

Following this, the third goal of having the 'right skills & resources at the right time' received two strategy suggestions. The first one is start early with value identification, creation, and communication towards key stakeholders (B2). This is suggested to use when trying to build a network around the company. The second strategy is find a partner that covers for the lack of expertise needed (B2).

Strategies targeting the goal 'make intellectual property set-up'

The fourth goal 'make IP set-up', got one strategy suggestion: find out if biopharma product is patentable (technologically and compared with competition) (B7). By using this strategy, a better market understanding can be gained regarding patentability of the product.

Strategies targeting the goal 'plan & execute clinical trials'

The next goal 'plan & execute clinical trials', was targeted with four different strategies. The first one is communicate with FDA and EMA to make sure to get authorization to start clinical trials (B2). The second one is almost identical, except that it is now targeting CA and CEC: communicate with CA and CEC to make sure to get authorization to start clinical trials (B2). The third strategy is involve physicians to get the care perspective on how patients are treated (B2). Finally, the fourth strategy is involve KOLs to get advice on how to make a suitable design of trials (B2).

Strategies targeting the goal 'increase product development speed'

For the last goal 'increase product development speed', there were also four strategy suggestions. The first one is take end-game into account and plan according to relevant regulations (B2). The second strategy is find a partner that covers the lack of expertise needed (B2), which is referring to finding external actors that can provide resources. The third strategy is use a CMO or CRO to do some steps in parallel to speed up the development (B2). Finally, the fourth strategy is the same as for goal 5: involve KOLs to get advice on how to make a suitable design of trials (B2).

5-7 Cross comparison of company interview results

In this section, the answers to the research questions from the different company interviews will be presented and compared. By doing this, it is possible to see similarities and differences in the answers from the different biopharma companies. Table 5-9 shows an overview of the answers from the companies, per sub question. The companies are represented by C1, C2, C3, and C4, referring to company 1, 2, 3 and 4.

As can be seen in table 5-9, all the sub questions have received some answers from each company. In total, the companies have described six main goals that the companies should aim for in the valley of death. These goals are: (1) develop the right product, (2) find sufficient funding, (3) right skills & resources at the right time, (4) make intellectual property (IP) set-up, (5) plan & execute clinical trials, and (6) increase product development speed. Compared with previous research methods, the goals mentioned there are the ones also mentioned here in the biopharma company interviews. All the companies also estimate the length of the valley of death to be around 10 to 15 years.

The second sub question was well answered with many actors and factors from each company. Many of them were similar and can be seen in several of the interviews, which is a good verification that these actors and factors are relevant. Of course, this also has to do with the fact that all interviewees were presented with the same set of cards during the interview. All identified actors and factors could be split to fit into the six different categories that were also used in the previous research methods.

Regarding the interconnections between actors and factors, the company interviews returned at least some interconnections for each goal. Overall the findings complement each other and are not contradictory.

The last sub question returned strategy suggestion for all goals in total. However, sometimes the strategies have very different perspectives for targeting the same type of issue. This is an indication that there are different ways to deal with the issues in the valley of death, and that it comes down to what the company and managers in the company prefers as a solution. One irregularity between the companies is that company 3 did not provide that many strategy options to deal with the different goals in the valley of death. The goals that were targeted with strategies from company 3 were 'develop the right product' and 'plan & execute clinical trials', and not so much on the resource perspective that the other goals are about. However, the other companies compensated for this by providing a broad span of strategies covering all the goals.

Table 5-9: Overview of cross comparison of company interview results

		C1	C2	C3	C4	Remarks
SQ1	Time frame VoD (years):	10	10-15	10-15	10	All companies estimate a similar time frame of VoD, between 10 to 15 years. All companies mention five to six main goals, which are all similar.
	Goal 1: Develop the right product	X	X	X	X	
	Goal 2: Find sufficient funding	X	X	X	X	
	Goal 3: Right skills & resources at the right time	X		X	X	
	Goal 4: Make IP set-up	X	X	X	X	
	Goal 5 Plan & execute clinical trials	X	X	X	X	
	Goal 6: Increase product development speed		X		X	
SQ2	Number of actors defined:	18	19	21	19	Similar responses in what actors and factors were defined. All companies provided actors & factors in the same six categories.
	Number of factors defined:	19	23	27	20	
SQ3	Interconnections goal 1	X	X	X	X	The different company interviews complement each other well on this research question, so overall all the goals has some related interconnections described. Moreover, there was also at least one company that covered each of the four sub phases in the valley of death with some in-depth explanations and a visual picture.
	Interconnections goal 2	X	X	X	X	
	Interconnections goal 3	X		X	X	
	Interconnections goal 4		X		X	
	Interconnections goal 5	X	X	X	X	
	Interconnections goal 6	X	X			
	Picture from the sub phase 'discovery & R&D'	X	X		X	
	Picture from the sub phase 'pre-clinical testing'		X			
	Picture from the sub phase 'clinical trials'	X		X	X	
	Picture from the sub phase 'launch preparation'			X		
SQ4	Strategies goal 1	X	X	X	X	Company 1, 2 and 4 provided strategies to all the respective goals from those interviews. In total, there is an overlap so that all goals are targeted with strategies. Moreover, the interviews in company 1,2 and 3 provided some additional strategies that could not be coupled to the goals from the respective interviews.
	Strategies goal 2	X	X		X	
	Strategies goal 3	X			X	
	Strategies goal 4	X	X		X	
	Strategies goal 5	X	X	X	X	
	Strategies goal 6		X		X	

Chapter 6

Results

In this Master's thesis, three different research methods have been used in order to find answers to all the stated research questions in section 1-6. The literature provided information more from a historical and academic perspective, whereas the Vintura interviews and biopharma company interviews contributed with a more practical approach towards the research questions. This chapter aims to consolidate all findings from chapter 2, 3 and 5 and make final answer to the research questions. In section 6-1, the approach for the analysis of all results is described, explaining what steps were taken and the reason behind. In section 6-2, the final answers to the research questions will be presented, which contains elements from all of the three research methods in this thesis, also including an answer to the main research question. Finally, in section 6-3 the model created from all the results will be presented and explained, followed by a short case example of strategy selection and a matrix showing potential interferences between goals.

6-1 Approach to make the analysis

Several steps were followed for making the full analysis of all information gathered from the three methods: literature review, Vintura interviews, and company interviews with biopharma firms.

In order to consolidate the answers for the first sub question, all the information from the three research methods was compared and combined. Some general phase characteristics could be seen, e.g. that the time frame of the valley of death is 10 to 15 years. Moreover, there were six goals in total from all the research methods. These together covered for all the goals mentioned in the three research methods, where many answers from the three methods overlapped.

For the second sub question, all the identified actors and factors from the different research methods were compared. Initially, it was important to make a suitable categorization of actors and factors in order to sort and make sense of all information. Already during the literature study the decision was made on what categories to use, and they proved to work

for the other two research methods as well, since all actors and factors could be placed into these categories. Since the same methodology was used for all the biopharma interviews, many actors and factors were mentioned in several interviews. This is because the cards with the actors and factors were reused for each interview, with the possible addition of new cards if the interviewee added new information. During each interview, the interviewee was asked to select the key actors and factors from the set of cards, and then relate them. This means that some cards per interview were not used, since they were not considered key by the interviewee. But for each new interview, the interviewee was always presented with a full set of cards. In each results section of all research methods, the actors and factors were also related to the main goals. These answers were consolidated into one story, by adding all information together and comparing it, in order to reach a final answer to the second sub question.

Regarding the third sub question about interconnections, each research method returned answers summarized in tables, where actors and factors linked to each main goal were listed, and their relations explained. These tables were all compared in order to create one final table with the important interconnections. Many of the relations explained were also found in other research methods, so the task to add them together was not too tricky.

Finally, the last sub question about strategies was analyzed and answered by comparing and adding together all strategies per main goal. Sometimes the strategy perspectives were very different and even opposing, but this was not a reason for excluding a strategy. On the contrary, the different perspectives could be valuable when a manager is going to select a strategy, since the broad range increases the chances that managers can find a strategy fitting to their company approach.

In order to visualize the relations between actors and factors, and to see whether they have a facilitating or blocking effect to reach the main goals in the valley of death, a theoretical model was created. The model shows relationships between facilitators, barriers, and strategies to use to target the barriers. In section 6-3 below, the model will be further elaborated on.

6-2 Consolidated answers to research questions

This section contains the final consolidated answers to all sub questions in this thesis. The approach to the analysis of all results has been explained in section 6-1, and here is the final outcome of that. In other words, all the information in the results sections from all three research methods have been combined to create answers to the four sub questions. In section 7-1, the explanation on how these four sub questions help to answer the main research question is described.

SQ1: *"How does the phase between invention to a first market introduction look like for biopharma companies?"*

The first sub question is quite broad and exploratory, investigating how the phase also known as the valley of death looks like for biopharma companies. The answer to this question is split up in two parts: (1) what are typical phase characteristics of the valley of death, and (2) what are the main goals that biopharma companies should aim to achieve in the valley of death.

Phase characteristics of the valley of death

All research methods above generated a uniform result regarding the time frame of the valley of death. It was described that it takes between 10 to 15 years to complete the phase (V1, V4, B8, B5, B6, B3, B4, B2, Reed (2011), Hudson and Khazragui (2013), Frank, Sink et al. (1996)). The phase is very strictly regulated (B2) and contains much uncertainty and risk for a biopharma firm, e.g. regarding developing the right product or getting access to sufficient capital (V2). However, initially the company does not have much competition since different companies head in various directions with the product development (V2, V4). Only if companies target the same disease area, a direct competition situation can occur (V1, V2, V4, V5). Overall risk management is needed, but a firm can also choose to share the risk with partners in collaborative set-ups (B8). On the other hand, it is also important that a biopharma firm dares to take calculated risk in order to get through the valley of death with an innovative product as the end-result (B6). Since the biopharma industry is risky in general, both regarding technology and market, it is required that a firm takes risk to create an innovative product, but it should be a risk that is estimated and accounted for. Pursuing clinical trials is an incredibly difficult and expensive part of the valley of death, and sometimes it is underestimated how much resources are required for this in comparison with doing discovery and R&D activities (B2). There are very few ideas that will make it through the valley of death to become a final product; about 1 to 3 ideas out of 1000 makes it all the way (B2).

Main goals in the valley of death

From the three research methods there were six main goals defined that companies should try to achieve in the valley of death. Different combinations of these six goals were mentioned in all the three research methods, with quite some overlap between the results. Figure 6-1 shows an overview of all six goals: (1) develop the right product, (2) find sufficient funding, (3) right skills & resources at the right time, (4) make IP set-up, (5) plan & execute clinical trials, and (6) increase product development speed. By aiming for these goals, the biopharma firms can have a higher chance to survive in the valley of death. Using these six goals is a way to compress the extensive amount of information from the three research methods, and distilling the key elements. In the following paragraphs there will be an explanation of each goal more in detail.

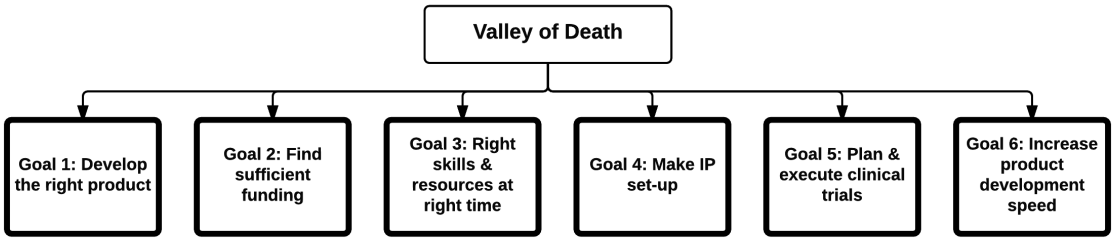

Figure 6-1: Overview of main goals in the valley of death

Goal 1: Develop the right product

The first goal is about developing the right product in terms of what the market and patients require (B1, B5, B8), but also making sure it is interesting from a scientific point of view (B2, B5). The final drug must live up to the safety and efficacy requirements (B5, B6), and must be feasible from a production and cost perspective when compared to current treatments in the market (B4, B6). If the product has any potential commercial issues, e.g. the taste of the medicine or lack of understanding the complexity in the pharmacokinetic profile, they will most likely be discovered in the clinical phase and should be dealt with immediately (B1, B2). In general, a biopharma firm has limited resources and therefore fewer candidates in the process, making it extra important to focus the resources on creating a clinically differentiated product that targets an unmet medical need (B4, B5).

Goal 2: Find sufficient funding

Generally, a biopharma firm has a resource-constraint, which means that the firm needs to make a drug development plan based on existing resources and knowledge (B5). A biopharma firm needs to focus on finding sufficient funding to survive the long and expensive valley of death, since there is not yet any sales revenue for the new product (B1, B5, B6). There is a great need for capital to fund the further R&D activities (B1), and when the firm reaches the clinical phase, the need for more capital has drastically increased (B2). One way to get capital is through government funding, in a pre-competitive stage, where a group of firms can receive money to turn a technology into application. For the next financing step, large firms might be able to allocate funds internally (B3), but most smaller firms need to reach out to external investors and prove that the product has enough potential (Reed 2011). Since this is an uncertain position for investors, they might be hesitant to invest in these kinds of projects that are very capital-intensive (Frankel 2012). There are very few investors with an appetite for these high-risk projects (V2), which is why most investors become interested in investing when the risk profile is more stable, i.e. when more concrete results from the drug development process are established (V2, V4, V5).

Goal 3: Right skills & resources at the right time

The biopharma firms need to focus on having the right skills and the right resources throughout the valley of death, since the need will change due to the different activities that are

carried out in this phase (V1, V2, V3, V5, B1, B8). It is common that a biopharma reaches out to suitable partners that can complement the need of other resources and knowledge (V2, V3, V5, B3). This is especially true during the clinical phase, since it requires many different types of resources (B2). Having a good network around the company can offer flexibility and support, since if another development path seems better, the company can reach out to actors in the network (V4).

Goal 4: Make intellectual property set-up

The next main goal is about intellectual property set-up, meaning that it is important that a biopharma firm decides on a set-up that aligns with the company goals and with the technology or product itself (V1, V2, V5, B3, B5, B6). A large part of the value in a biopharma firm is from the intellectual property and the in-house talent (B7). Sometimes, a biopharma product is not patentable by law (e.g. some human proteins) (B2), but if the production process is very complicated it can already create enough of a hurdle to keep it protected (V5, B7). When a biopharma is working with partners, it is important to make a contractual agreement upon intellectual property ownership (V5, B3). In order to make a successful patent filing, the product must be innovative and there cannot be too much information about it disclosed in the public domain, which is why IP set-up should be discussed early in the product development process (B2, B5, B6).

Goal 5: Plan & execute clinical trials

In order to test the drug candidate further, the company must enter the clinical phase, which is where the clinical trials take place (V5, B1, B2). The clinical phase is very expensive, and is very critical since the biopharma firm can either make it or break it here (B2, B3). Compared with the discovery and R&D phase, the clinical phase is much more business-oriented, meaning that the R&D focus must shift into focusing towards the launch of the product (V5). It is a complex process to plan, set up, and execute the trials, including many actors and activities, and the biopharma firm usually seeks support for this (V5, B1, B2, B6). There is an interaction between the regulatory authorities and the biopharma firm when setting up the trials and to get approval to start the testing (B4).

Goal 6: Increase product development speed

Finally, the last goal for biopharma companies in the valley of death is to try to increase the product development speed in order to get a product as quick as possible to the market (B2). It is a clear advantage to be first to the market, especially with an innovative product targeting an unmet medical need, and therefore it is smart to try and speed up the development (B6). A biopharma firm must understand if some steps can be done in a faster way (V5), although some steps are required from a regulatory point of view, making it hard to affect the speed (V5, B6). Bringing in a partner can potentially increase the speed due to the added capabilities that a partner can offer (V5).

SQ2: *"What are the key actors and factors in this phase that affects the performance of the biopharma companies?"*

In order to answer this second sub question, all the previous answers to this question were combined into one answer, which is described in the following paragraphs. The actors and factors are related to each of the six main goals identified in the first sub question. The information from all the three research methods was complementary and sometimes overlapping, but there were no critical oppositions that created a blockage towards finding a consolidated answer.

Actors and factors for the goal 'develop the right product'

During the process of developing the right product, there are many actors and factors involved. Some of the factors are related to the technology or product itself, e.g. describing important properties of the product. The first one is cost-effectiveness of technology, which is important when comparing the potential of the product towards current treatments (V5, B4, B6, B8). If a product is too expensive compared with what is in the market it will not be feasible, although it might have a high innovative value (B1). Secondly, the technology safety is crucial to consider during the product development (B4, B5, B6), since it is obvious that a product that lacks safety will not pass the regulatory approval. The third critical factor is concerning commercial issues with the product, since these issues needs to be tackled in time (B1, B2, B6). Commercial issues are usually discovered during the clinical phase, and can be e.g. unexpected side effects like dry a mouth after taking the drug (B1). It is important to have an overall project manager, during the drug development phase, with leadership skills (V2, B1, B2, B4, B6), since one task is e.g. communicating commercial issues to other actors in the company (B2). Moreover, being able to be self-aware and self-critical are also skills that a biopharma firm need to make the right decisions (V2, B5, B6, B8). There are two factors that positively influence the process of developing the right product. The first one is that the product should have some business attraction to be more promising (B2), and the second one is that the cost of goods should be manageable (B3, B6).

Furthermore, from a market perspective, a biopharma firm can benefit from advice from insight generators (B6), key opinion leaders (V2, V4, V5, B8), patients (B3), and Patient Advocacy Groups (B2). It can also be advantageous to have a large home market, meaning the local market, but it is not a requirement (V2, B2). It is critical that the firm has market understanding to know what product to aim for to benefit the patients (B5, B6). The HTA agencies use different market access criteria to evaluate whether a product should be granted market authorization, so it is therefore important to be aware of this process (B4). Policymakers can influence what products are beneficial to produce by their allocation of spending towards a certain disease area (B4). Finally, checking the plans for the product development with FDA and EMA at an early stage is recommended (B6).

Actors and factors for the goal 'find sufficient funding'

For the second goal, find sufficient funding, the obvious key factor is having access to capital (V1). There are several external actors that a biopharma firm can reach out to in order to

get capital. The first one is external investors, e.g. venture capitalists or private equity firms, that can provide access to capital but sometimes also relevant knowledge or other capabilities that a firm might need (V1, V2, V5, B2, B3, B5, B6, Frankel (2012), Frank, Sink et al. (1996)). There is a scarcity of investors that have an appetite for really high-risk projects, such as drug development, meaning that the firm needs a convincing story (V2). Another possibility is to reach out to academia for grants (V2). The third option is to talk with big pharma firms to see whether an agreement can be set up, or if the big pharma firm wants to acquire the biopharma firm (V1, V5, B1, B5). The big pharma firm can provide valuable experiences and capabilities regarding drug development. When a biopharma firm reaches out to a potential partner, it is crucial to have skills of professionalism and business sense to know how to value the firm and what information to present (V2, B2, B8). Furthermore, the firm needs good communication skills to make a successful contact with a potential investor (B8). Finally, a good network around the firm can provide an advantage when the firm is looking to raise capital (B5, B6).

Actors and factors for the goal 'right skills & resources at right time'

Due to the characteristics and the length of the valley of death, the biopharma firms need to have the right skills and resources at the right time in this phase. It is helpful to have an entrepreneur with good relationship management skills that can focus on building external relations around the firm (V5, B6, B8). Another thing that can positively influence the goal is to have access to support resources such as academic incubators that can offer knowledge and advice (V5, B3, Bessiere, Gomez-Breysse et al. (2014)). A strong network around the company is critical, (V4, V5, B8) since it offers the biopharma firm the flexibility to reach out to other partners if the product development is taking another path (V4). Internally in the firm, a good project manager with communication skills is needed to align the internal actors on e.g. risk management and intellectual property set-up (V5, B4). Moreover, working with a suitable partner can provide access to human resources needed in the valley of death (V5, B4, B6, B7, B8, Markham, Ward et al. (2010)). Complementary technology providers are critical to bring in for technological resources (Clark 2013), e.g. in production support (B1, B6).

Actors and factors for the goal 'make intellectual property set-up'

The fourth goal is to make an appropriate intellectual property set-up that needs to fit with the company and also to protect the product and/or production process in the best possible way (B1, B3, B8). It is common that a biopharma firm is not an expert on intellectual property regulations, and it can therefore help the firm to bring in external advice about this in order to avoid beginner's mistakes (B6). Moreover, in order to make a good IP set-up it is crucial to have market understanding, meaning knowing what the competition is patenting and therefore finding out what is innovative and can therefore be patented (B5). The timing of a patent application is a critical decision point, due to the limited scope of a patent of 20 years (V1). There will be a balance of disclosing information and the risk that someone else steals the idea when deciding on how to set up the IP protection (B1). It is critical that a project manager, in collaboration with regulatory affairs, makes a solid decision on when to file a patent (V1, V5, B2).

Actors and factors for the goal 'plan & execute clinical trials'

The clinical phase is very complex and therefore requires extensive planning and a good execution, with a suitable project manager internally in the biopharma firm that can have the overview (B1, B2, B4, B6). Before starting the clinical trials, a biopharma firm needs to get formal authorization from FDA and EMA to start the testing (V3, V5, B2, B3). In addition to this, the authorities Competent Authorities and Central Ethics Committee also have regulations that a biopharma must follow to get an approval for pursuing the trials, also from an ethical point of view (B1, B2). The policymakers are influencing what products and disease area are beneficial to target, by allocating their spending in a certain disease area (B4).

The design of the clinical trials is a crucial factor where everything is tied together in one plan (V5, B1, B2, B3, Adams (2012), Roberts, Fischhoff et al. (2012)). It is important to design the trials according to the market access criteria from the Health Technology Assessment agencies, which are criteria they use to evaluate if a product should be approved in the market or not (V3, V5, B4). Moreover, reaching out to Key Opinion Leaders to get input on the planning and the trials design can positively influence the success rate of the clinical trials (V2, V4, V5, B1, B4).

It is critical to have access to working with the right hospitals and physicians in order to get access to patients (V5, B1, B2, B3), whom are the actual study objects for the drug testing (V2, V5, B3). The biopharma firm needs clinical scientists for carrying out the clinical work (V5, B3, B4). To get support with the execution of the trials, a biopharma firm can choose to work with Contract Research Organizations that can help with the operations and management of the trials (B1, B3, B5, B6). Moreover, Contract Manufacturing Organizations can support with the manufacturing process for the drug, or even producing the drug for the biopharma firm (B3, B5, B6). If a biopharma firm wants to understand better what treatments are actually used for certain diseases, it can be smart to bring in clinician-scientists that are doctors who also carry out scientific research (V5, B6).

Actors and factors for the goal 'increase product development speed'

Finally, the last goal is to increase the product development speed in the valley of death. It is crucial for a biopharma firm to consider the relevant regulations in the phase and adapt the product development to them in order to decrease the probability to have delays (B2, B6). The firm must make sure to work with suitable partners such as complementary technology providers, in order to get access to e.g. technological resources (V5, B6). It is also important to make sure to have sufficient supply of the drug for both clinical purposes as well as to sell in the market later on, which is an aspect often neglected or taken for granted by the firm (B3). Moreover, if the design of the clinical trials is good, the operations will run smoother and the risk of delays is lower (V5, B6). The factors 'commitment' (B6, B8) and 'information technology (IT)' (B1, B2) can both have a positive contribution towards speeding up the trip through the valley of death.

SQ3: *"How are the actors and factors in this phase interconnected?"*

This research question has been summarized in table 6-1 with an overview of all the six goals, the related actors and factors, and the obvious relations between these, as described in the results above. Throughout this thesis report this interconnections table has been created individually from all research methods, by an interpretation of all information found. These tables were compared in order to create table 6-1, which contains the compiled answer including all interconnections mentioned. Overall, there were no directly contradictory answers, but rather complementary or similar answers that together provide a more extensive picture of what happens in the valley of death, compared with the three methods individually.

Table 6-1: Summary of author's interpretation of interconnections as an answer to SQ3 in the thesis

Main goal	Actors	Factors	Relation
1. Develop the right product	Project manager, insight generators, patients, Patient Advocacy Groups, KOLs, HTA agencies, FDA, EMA, policymakers	Business attraction for product, cost-effectiveness of technology, self-awareness & self-criticism, market access criteria, market understanding, leadership skills, product safety, commercial issues, large home market, cost of goods, advice, regulations	Advice from insight generators, KOLs, patients and Patient Advocacy Groups can help a biopharma firm. A project manager needs to have leadership skills. Moreover, HTA agencies work with market access criteria to evaluate the product. Policymakers set the rules and regulations, and FDA and EMA can be involved early to check the plans and give advice.
2. Find sufficient funding	Investors, academia, big pharma firm	Access to capital, professionalism & business sense, communication	Access to capital can come from external investors, academia or a big pharma firm. The biopharma firm needs to have professionalism & business sense and communication skills when reaching out to investors.
3. Right skills & resources at right time	Suitable partner, project manager, entrepreneur, complementary technology providers	Human resources, communication, network around company, relationship mgmt. skills, technological resources, support resources	An entrepreneur with relationship mgmt. skills can reach out to external stakeholders, while a project manager with communication skills can align internal needs for resources. Suitable partner can provide access to human resources, and complementary technology providers access to technological resources.
4. Make IP setup	Project manager, regulatory affairs	Realizing when patent should be filed, market understanding, advice, IP regulations	A biopharma firm can get external advice on IP regulations. Internally, a project manager together with regulatory affairs should realize when a patent should be filed.
5. Plan & execute clinical trials	Project manager, clinical scientist, clinician-scientist, CROs, CMOs, hospitals, physicians, patients, FDA, EMA, CA, CEC, KOLs, policymakers, HTA agencies	Design of clinical trials, market access criteria, access to patients, manufacturing process, regulations, advice	FDA, EMA, CA and CEC give a biopharma firm authorization to start clinical trials. Policymakers also have regulations that need to be followed. The project manager needs to work with hospitals and physicians to get access to patients. KOLs can give advice about planning and design of clinical trials. HTA agencies work with the market access criteria. A CMO can do the manufacturing of the drug for the biopharma firm.
6. Increase product development speed	Suitable partner, complementary technology providers	IT, regulations, design of clinical trials, commitment, clinical & market supply, technological resources	Complementary technology providers can offer technological resources to a biopharma firm.

SQ4: *"What are strategies for biopharma companies to deal with this phase?"*

All the three research methods returned strategies that can be coupled to the main goals, and even to specific issues within each goal. These have all been elaborately explained in respective section: 2-2-4 for the literature, 3-2-4 for the Vintura interviews, 5-3-2 for company 1, 5-4-2 for company 2, 5-5-2 for company 3 and finally 5-6-2 for company 4. The strategies are also included in the final model for the valley of death, which is presented in section 6-3. For these reasons, the strategies are not further explained here but rather just listed per goal, with the specific reference to show where the strategy was identified. To clarify further, these lists are summaries of all the strategies suggested throughout the report, coupled to specific goals in the valley of death.

Strategies for develop the right product

1. Make sure the product is clinically differentiated (B4)
2. Make sufficient testing of the product to ensure safety (B5)
3. Take all signals seriously that the drug is not safe (B4, B5)
4. Evaluate knowledge gained in clinical trials and tackle issues (B1, B2)
5. Predict future technology and patient behavior and needs (B3)
6. Be forward-looking in the approach (V5, B3, B5, B6)
7. Communicate between company departments (V3)
8. Understand the patient needs to see where to add value (B4)
9. Have insights in the competitive landscape (B4, B6)
10. Bring in relevant experts on day 1 (V4)
11. Go for the most difficult questions first (V2)
12. Make sure to have a good project manager in charge of the product development (B4)
13. Adapt the product to fit with current regulations (B6)

Strategies for find sufficient funding

1. Have a strong person internally that can reach out to and communicate with investors (V1, V2, B1)
2. Seek investors that bring in knowledge and network (V2, B6)
3. Use crowd-sourcing for capital and competence (Girdauskiene, Venckuviene et al. 2015)
4. Go public with the shares of the firm to gain capital (B2)
5. Make sure to have a good and scientific sound story (B2, B6)

6. Reach out to academia for grants (V2)
7. License out the product to big pharma (B5)
8. Make sure risk profile is interesting for big pharma to invest (V5)
9. Make sure the idea is protected with a good IP set-up (B5)

Strategies for right skills & resources at right time

1. Reach out early to key stakeholders (V2, V3)
2. Combine parties with overlapping networks (V4)
3. Make sure to have people internally that are able to build external contacts (B8)
4. Start early with value identification, creation, and communication towards key stakeholders (B2)
5. Make sure to have persons internally with good communication skills (B8)
6. Find a partner that covers the lack of expertise needed (V5, B2, B5, B6)

Strategies for make IP set-up

1. Find out if biopharma product is patentable (technologically and compared with competition) (B7)
2. File patent early and then talk openly about the idea (B5, B8)
3. Don't use patents in order to keep trade secrets (B1)
4. File patent as late as possible to maximize the use of the patent scope (V5)

Strategies for plan & execute clinical trials

1. Understand market access criteria that HTA agencies are using to evaluate the final product (V5)
2. Know how the authorities evaluate the end-result and plan accordingly (B1)
3. Communicate with FDA and EMA to make sure to get authorization to start clinical trials (B2)
4. Communicate with CA and CEC to make sure to get authorization to start clinical trials (B1, B2)
5. Use capabilities of partners (e.g. CRO) to manage the execution of clinical trials (B6)
6. Make sure to have a good project manager in charge of the clinical trials (B4)
7. Make sure to have clinical scientists who can execute the trials (B4)

8. Find the right hospital and physician to work with in order to get access to patients for the trials (B3)
9. Involve physicians to get the care perspective on how patients are treated (B2, B4)
10. Involve KOLs to get advice on how to make a suitable design of trials (B2)
11. Design the clinical trials according to market access criteria (V5)
12. Include the right comparator in the design of clinical trials (V3)

Strategies for increase product development speed

1. Make sure to have sufficient supply of the drug, both for clinical trials and for the market launch (B3)
2. Take end-game into account and plan according to relevant regulations (B2)
3. Find a partner that covers the lack of expertise needed (V5, B2, B5, B6)
4. Use capabilities of partners to speed up the development (V5)
5. Use a CMO or CRO to do some steps in parallel to speed up the development (B2)
6. Use drug re-purposing in order to reduce the number of pre-clinical tests (Sem 2014)
7. Involve KOLs to get advice on how to make a suitable design of trials (B1, B2, B4)
8. Design the clinical trials according to market access criteria (V5)
9. Include the right comparator in the design of clinical trials (V3)
10. Use adaptive clinical trials (B3)
11. Lower the investment per treatment in order to test more (B3)
12. Use hit-to-probe-to-lead strategy in order to plan smart trials (Roy, Taylor et al. 2009).

6-3 Model creation

As an end result of the thesis research, a theoretical model to visualize the relationships between actors, factors and strategies in the valley of death was created. The model shows the six main goals for a biopharma company in the valley of death, and also shows detailed relationships for actors, factors and strategies within each goal. In order to understand the environment that a biopharma firm experiences in the valley of death, a market model was developed to show the main actors that are involved. Subsection 6-3-1 presents the market model, the following part, subsection 6-3-2, describes the theoretical model more explicitly by elaborating on the components of the model. Finally, the detailed sub models per goal are presented and described in subsection 6-3-3.

6-3-1 Market model for the valley of death

In order to further understand how a biopharma company experiences and deals with the valley of death, it is useful to see the other actors involved in the market. There are several ways to describe this external company environment, where the marketing Professor Philip Kotler has provided some well-renown models that show this. Professor Kotler has an economist view of how marketing is linking society and industry. One overview of a company in its environment can be seen in figure 6-2. This is a marketing system that shows the interactions between a company and the suppliers, competitors, intermediaries and the market (Kotler 1971). The whole system is influenced by economics, public policy, technology and culture.

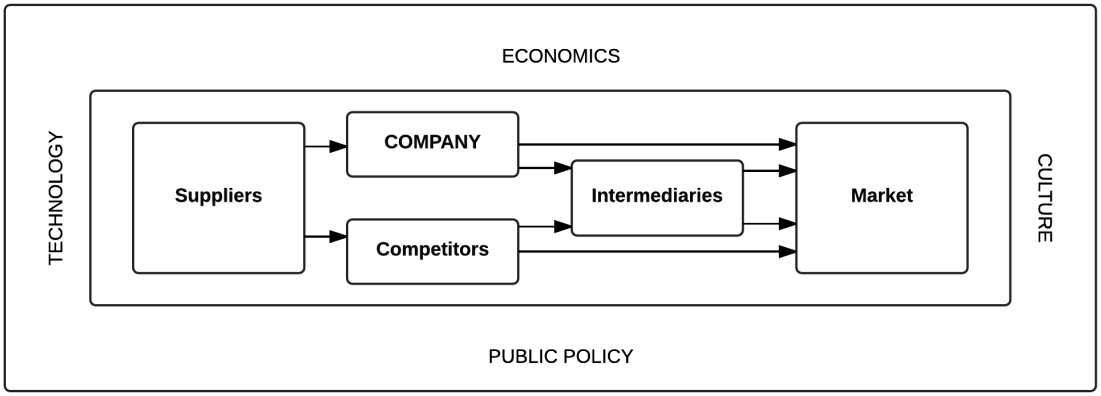

Figure 6-2: A marketing system (Kotler 1971)

In a later book by Kotler, this marketing system is developed even further to a national level. In figure 6-3 there is an overview of major participants and forces in a national marketing system. In the upper part of the figure, there are macroeconomic forces such as economic, technological, and political. In the lower part of the figure there are publics, such as financial actors, media, or government. In the middle there are different types of actors presented in four categories: (1) resource suppliers, (2) manufacturers, processors, (3), distributors, facilitators, and (4) consumers (Kotler 1980).

From the same book by Kotler, he also specifies this environment from a company perspective, which is seen in figure 6-4. Here the different levels in the marketing environment are displayed, with the relative distance to the company (Kotler 1980). The levels with macro-environment and publics are the same as described for figure 6-3, but the difference here is that the company is the focus point.

For this thesis research another market model was created, inspired by the three figures just mentioned. The reason that another model was created was to suit the specific environment in the valley of death, with a focus on biopharma companies. The result is a more detailed market model with specific actors mentioned that need to be understood to use the more detailed theoretical model showing actors, factors and strategies, presented in the next subsection. The created market model can be seen in figure 6-5, where the company is highlighted to show that this model is centered on the company perspective. The full lines in the figure are drawn between actors in the supply chain, meaning that there is a direct and close relationship

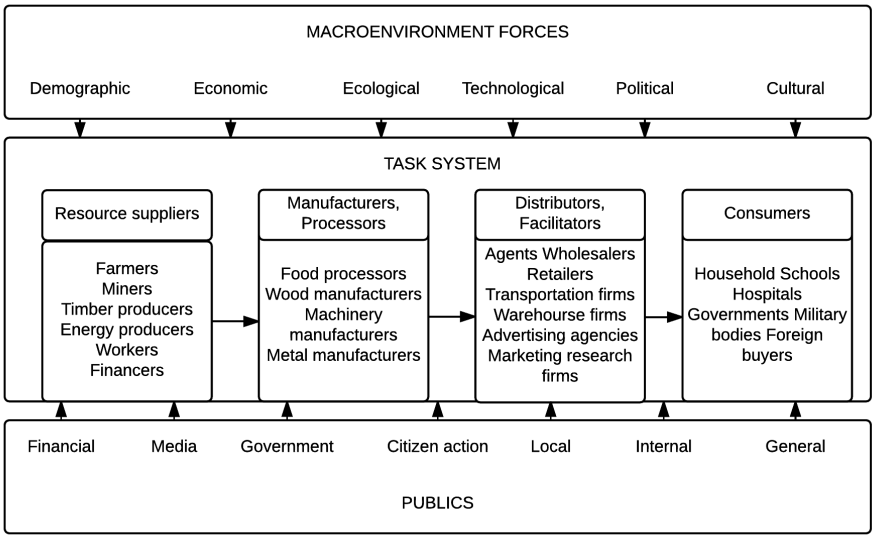

Figure 6-3: Major participants and forces in a National Economic System (Kotler 1980)

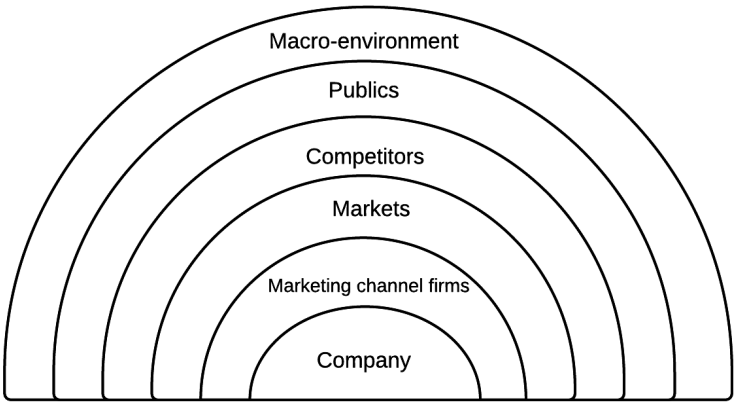

Figure 6-4: Levels in the marketing environment of a company (Kotler 1980)

between these actors. The dotted lines represent different kinds of processes that take place between actors, e.g. the flow of information, knowledge, or capital.

This market model shows, in the middle, the horizontal supply chain all the way from suppliers and investors, through intermediaries such as manufacturers and hospitals and finally reaching the patients, which are components inspired from the model in figure 6-2 by Kotler (1980). It is through the supply chain that the drug is created and delivered to the patients. The dotted line between external investors and the company represents the process where capital is received from investors. The competitors are added as an actor that is also targeting the final users, on the basis of the model by Kotler (1971). On the edge of the outside rectangle there are a few actors displayed that have an impact on the company but are not directly a part of

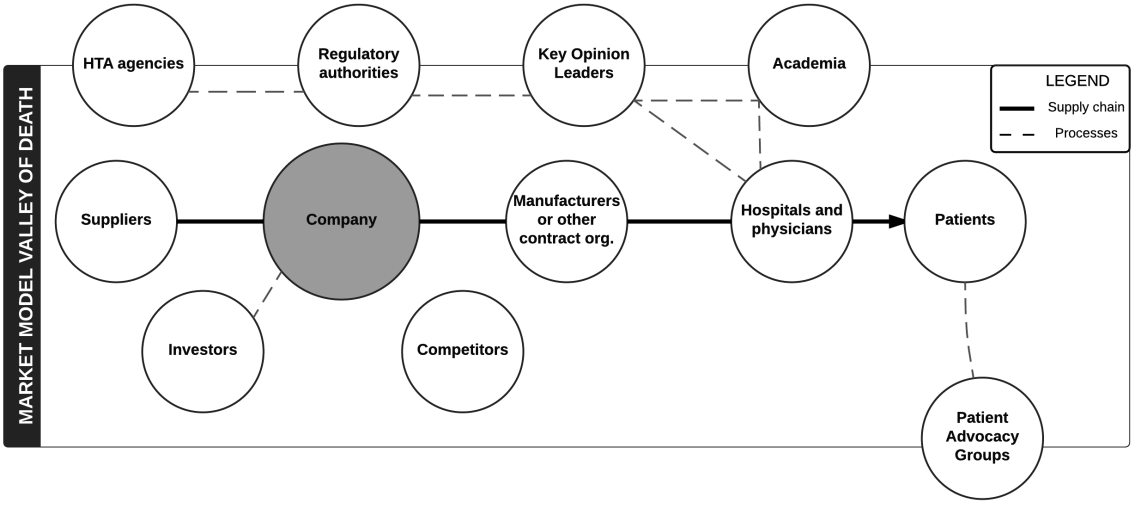

Figure 6-5: Market model for biopharma companies in the valley of death

its supply chain. This is the reason that they are displayed on the edge of the rectangle. The first actor is, from top left, HTA agencies that are carrying out health technology assessment of the drugs by using different market access criteria. In other words, they assess whether the final product from a company meets all requirements regarding e.g. safety and efficacy to be launched in the market, and based on this makes a recommendation to decision-makers whether to approve the final product or not. The next actor, regulatory authorities, are e.g. policymakers, FDA and EMA, and is added as an inspiration from the macro-environmental forces in figure 6-3 and 6-4 by Kotler (1980). These authorities are influencing the company by setting the relevant rules and regulations that must be followed. There is also a two-way link between HTA agencies and the regulatory authorities in terms of knowledge and advice from respective perspective.

The following actor is KOLs, who are experts in the field and can contribute with advice to the biopharma company. The KOLs are linked to regulatory authorities by also providing them with advice from the field. On the right, the KOLs are linked to the next actor, academia, where a lot of research activities take place and knowledge is generated. There is a triangular relationship between KOLs, academia and hospitals & physicians, shown in the figure. More specifically it means that some KOLs originate from the academia, e.g. professors in relevant topics. Moreover, there is a link between academia and hospitals because some hospitals are even called academic hospitals, meaning that there is a link to a university or other academic institution. Finally, the KOLs are also linked to the hospitals since they can give advice and have input on the clinical trials, which take place in hospitals. On the lower edge of the outside rectangle there is one more actor, Patient Advocacy Groups, who are linked to the patients, and represents organizations that can speak up and inform the outside world about the patient needs. Through this, these advocacy groups can influence the biopharma firm on what the patient perspectives are on a certain disease.

6-3-2 Theoretical model for the interactions in the valley of death

The research questions in this thesis are focused on exploring the valley of death and further understand the interconnections between actors and factors, and what strategies can be used to tackle the issues in this phase. As a result of all the three research approaches in this thesis, a final theoretical model was created to visualize relationships and contribute with a practical approach to show the answers to the different research questions.

From the thesis research it became clear that the biopharma companies have six different goals in the valley of death that needs to be achieved in order to get through the phase in a better way, see figure 6-6. It is important that one key assumption is made before the model can be used, which is: *the final product that is made is a drug or medicine.* This is important, since some of the goals are specific for the drug development process. Using these six goals is of course a way to simplify the complex valley of death and specifically understand the challenges for biopharma firms during this time period. In appendix B, a full overview of these goals and the related actors and factors can be found.

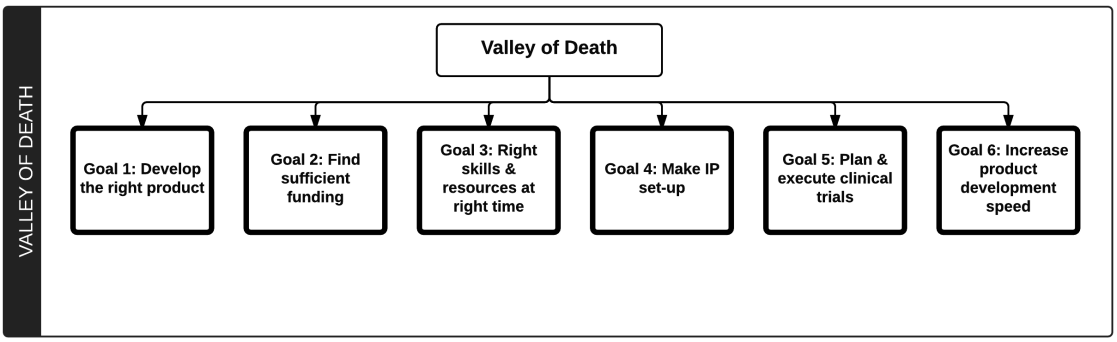

Figure 6-6: Overview of the six goals in the valley of death

In order to understand how the biopharma companies experience the valley of death, it was decided to decompose each of the goals and visualize what the interactions are within each goal. This might seem contra intuitive towards simplification, however it was decided to do so in order to make use of the practically oriented findings from this thesis. Since the concept of valley of death is broad and covers a time span of 10 to 15 years, it is interesting to see some concrete details to understand the mechanisms. Also from a company and managerial perspective, it is relevant to have concrete suggestions on how to deal with the goals specifically, in order to make the right choices to survive the valley of death. These are therefore the reasons to describe each of these six goals individually with their respective actors, factors and strategies.

In figure 6-7, there is a schematic overview of the theoretical model for one goal, with the various components shown. This will be used to explain how the model works, before presenting the specific sub models for goal 1 to 6. The model consists of four different components: (1) facilitators, (2) goal, (3) barriers, and (4) strategies towards barriers. The first component, facilitators, refers to things that have a positive influence towards the goal, i.e. contributes to reaching the goal. This can be an actor, a factor, or a combination of actors and factors that together works as a facilitator. The facilitators are important, but were not emphasized

as critical in the research findings. A facilitator is therefore less critical compared to the barriers, which is the third component that will soon be further explained. However, since the facilitators have a positive influence on reaching the goal, it is highly recommended for a biopharma company to consider these when solving the desired goal. In other words, the facilitators can be seen as a second priority to consider compared with the barriers, but the biopharma firm should not neglect them. The following component, goal, is representing the relevant goal for the model, which is one of the six goals from figure 6-6. The goal is the specific overall aim that should be achieved to deal with the valley of death in a better way. To solve the goal, the facilitators and barriers need to be considered and dealt with in the best possible way. The third component is barriers, which means things that are blocking the company from reaching the goal. As for the facilitators, a barrier can also be an actor, a factor or a combination of actors and factors that together works as a barrier. Since the barriers are blocking the goal, it is critical to tackle these in order to have a higher chance to be successful in achieving the goal. The barriers were emphasized in the research findings as more critical compared with the facilitators, but both components should be considered in order to have a higher chance of success. The fourth and final component is strategies, which are specific suggestions to use when dealing with a barrier. For some barriers there are multiple strategies suggested, representing different approaches to deal with a certain barrier. Choosing one strategy out of the options does not necessarily mean that another strategy is excluded. Since they represent different approaches, it can sometimes be valuable to follow several strategy suggestions for one barrier, as long as they do not interfere. This will become more evident when looking at the specific strategy options for a specific goal, in subsection 6-3-3.

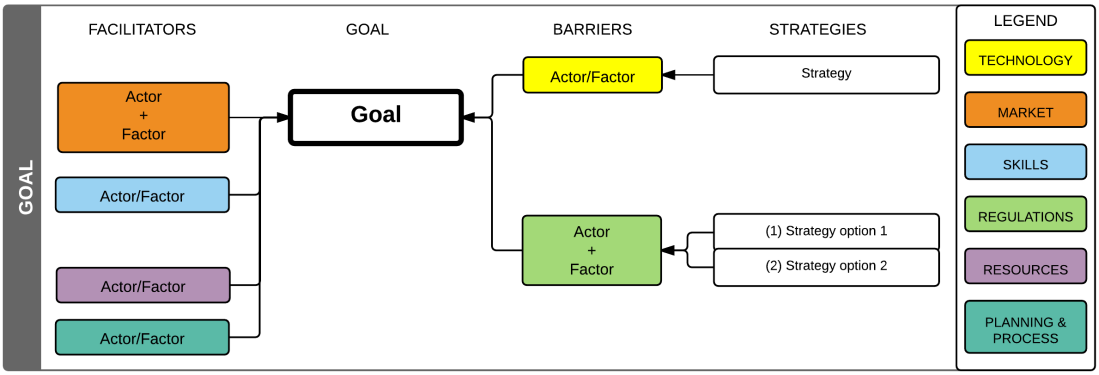

Figure 6-7: Schematic overview of the theoretical model and its various components

To the right in the schematic overview, figure 6-7, there is a legend showing six different areas in different colors that the actors and factors can be related to. The first one, technology, refers to anything that has to do with the product or technology itself, e.g. a property of the product or supply of the goods needed to make the product. The second area is market, which refers to actors and factors connected to the market model created for this thesis, presented in figure 6-5. The third area is skills, meaning different skills that are needed, e.g. communication skills. These can also be connected to a specific actor. The fourth area is regulations, which refer to the formal rules and regulations within the biopharma industry, and the actors that represent various authorities. The fifth area is resources, referring to different

types of resources that a company can utilize. This can be represented as a specific resource needed, e.g. support resources or can be an actor that together with a factor represents a resource, e.g. investors and capital. Finally, the sixth area is called planning and process, which refers to processes within the company. This can either be a single factor, but could also be an actor that is needed to make a certain decision for a plan or a process.

6-3-3 Specific sub models for each goal in the valley of death

In this subsection, the specific sub models for each of the six goals are shown and explained in detail. After all the models have been presented, an illustrative case is described to show how potential strategy choices for one goal can influence another goal. There is also a large matrix comparing the six goals with each other regarding what is a barrier and facilitator in certain goals, which can be useful to know when tackling several goals at the same time.

All the findings from the three research methods in the thesis project resulted in answers to the research questions, as presented in section 6-2. These answers provided emphasis that certain actors and factors are more critical in the valley of death than others. In order to further use the results and include them in the following six sub models, all actors, factors and strategies per goal were analyzed one level deeper, to see whether they could be distinguished as facilitators or barriers. More specifically, the information was analyzed and interpreted to see which actors and factors were described as the most critical (barriers) and which were described as less critical, but still important (facilitators). Through this, the actors and factors could be turned into facilitators and barriers per goal. Some actors and factors were clearly described to be either helping or blocking the goal, but sometimes it was more an indication, which then was interpreted in a suitable direction. The following paragraphs will present the outcomes of this analysis, and describe the facilitators, barriers, and strategies per goal.

Goal 1: Develop the right product

In figure 6-8, the overview of the sub model for goal 1 is presented. The first goal is to develop the right product, which means that it is not only enough to have an innovative idea but it also needs to fit into an unmet medical need in the market (B4). There are many stakeholders and factors to take into account when choosing what product candidates to brings further through the valley of death. From the results of this thesis, five different facilitators and eight barriers were identified to either help reach the goal or block it. For each barrier, certain strategies were suggested to overcome the blockade, which is why they will be presented for each barrier explanation.

The first facilitator is ‘business attraction for the product’, since if the product is promising from a business point of view it enhances the probability of the product to be successful later on (B2).

The second facilitator, ‘cost of goods’, can positively influence the choice of heading in a certain direction for the product development, since a lot of money could be saved here (B3). In other words, the cost of goods needs to be manageable; otherwise the product will never be able to compete with other treatments in the market (B6).

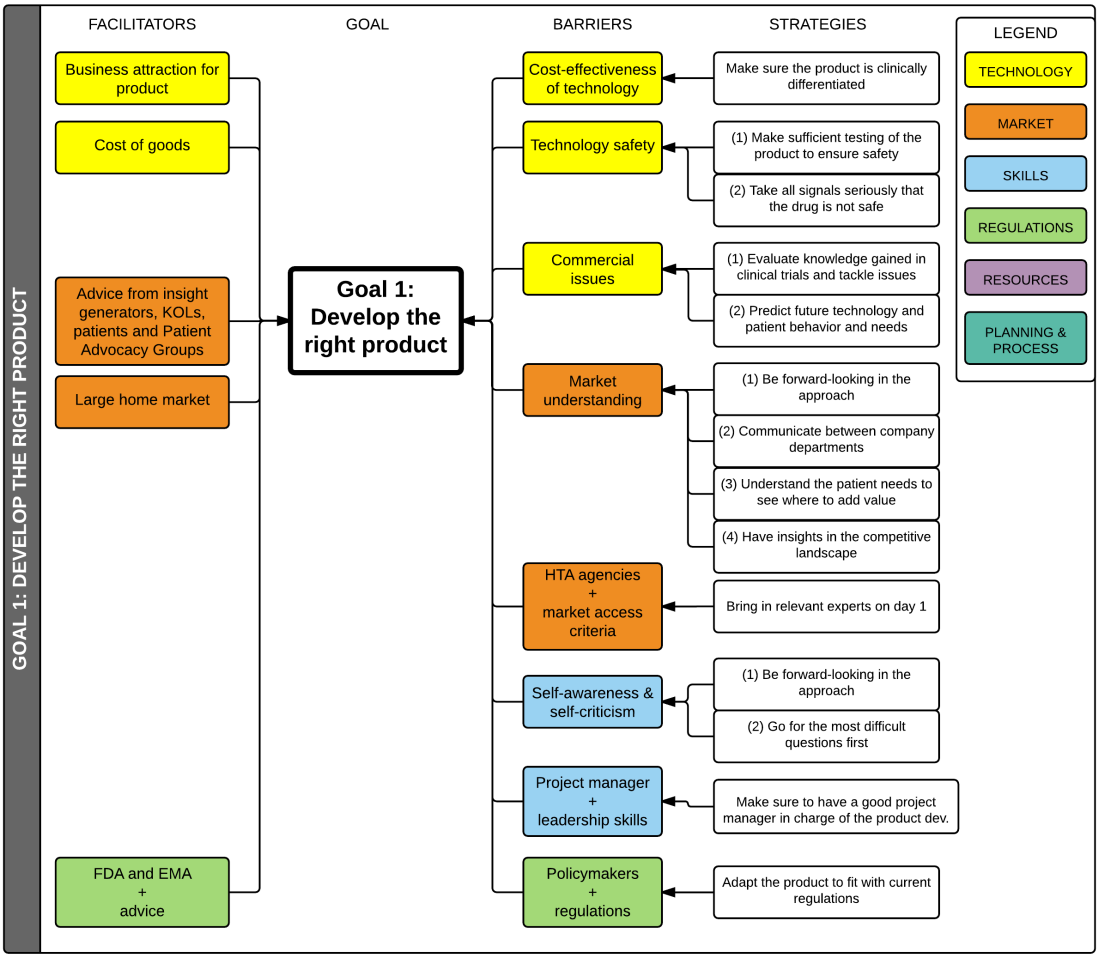

Figure 6-8: Goal 1: Develop the right product

Following this, the third facilitator is to get 'advice' from a few key stakeholders in the drug development process. It is important to understand where the unmet medical need is, and getting advice from 'insight generators' with various knowledge and functions can positively contribute to that (B6). 'Key opinion leaders' can give advice on the direction of the drug development (V2, V4, V5, B8). Another perspective is from the 'patients', since the final outcome is to add value for them, and therefore it is good to include their opinions (B3, Wong (2014)). If the biopharma firm cannot reach out to patients, it can go through 'Patient Advocacy Groups', which are organizations raising the voice about the patient needs (B2).

The fourth facilitator is having a 'large home market', i.e. the local market around the company. This is not a requirement, since biopharma firms usually operate internationally, but it can provide an advantage (V2, B2).

Finally, the last facilitator to develop the right product is to check whether the plans are realistic with FDA and EMA (B6). This should be done already early in the process so that the firm can adapt to their advice (B6).

Moving on to the barriers, the first one is 'cost-effectiveness of technology'. This refers to the

comparison of the drug with current treatments in the market, on a cost and effectiveness perspective (V5, B4, B6, B8). In other words, the drug will be evaluated with certain criteria to determine whether it is a better option than what is already in the market (Coller and Califf 2009). A highly innovative product is not enough if the product cannot show sufficient cost-effectiveness in the market (B1). The suggested strategy to deal with this barrier is to make sure that the product is clinically differentiated (B4).

The second barrier is 'technology safety', since it is crucial that the developed technology will have sufficient safety (B4, B5, B6). If a product is not safe, it will never get approval from the authorities and should not be developed further. The two strategies to tackle this barrier are to make sufficient testing of the product to ensure safety (B5), and to take all signals seriously that the drug is not safe (B4, B5).

The third barrier is 'commercial issues', which is a term that encompasses a few things. It refers to being aware of what products the competitors are making compared to the own products (Adams 2012), but is also about e.g. that the medicine has got a strange taste when being swallowed (B1). The commercial issues are therefore a barrier towards developing the right product, and should be dealt with in time (B1, B2, B6 Hudson and Khazragui (2013)). There were two proposed strategies for this barrier: the first one is to evaluate knowledge gained in clinical trials and tackle issues (B1, B2), and the other one is to try to predict future technology and patient behavior and needs (B3).

The next barrier is a combination of an actor and factor that together forms a barrier. More specifically this is about lacking a 'project manager' with 'leadership skills' that can speak up about the potential and benefits of an idea and try to take the company further (Frank, Sink et al. 1996). The project manager needs to have an overview of the whole drug development process, and needs leadership skills to manage it well (V2, B1, B5, B6). Leadership skills are also needed to be able to make the difficult decisions to stop or change the development plans(B4). The strategy to deal with this is to make sure to have a good project manager in charge of the product development (B4).

The fifth barrier is lack of 'market understanding' within the biopharma firm. This is needed in order to be sure that the right product is being developed (B5, B6, Coller and Califf (2009)). A good market understanding also means a good understanding of what the patients need, and therefore knowing how to add value (B5). For this barrier there were four different strategies suggested. The first one is to be forward-looking in the approach (V5, B5, B6), which means thinking ahead to the next steps continuously and following what happens in the market. The second strategy is to communicate between company departments (V3), meaning that information should be shared about market knowledge within the company. Thirdly, the next strategy is to understand the patient needs to see where to add value (B4), which contributes to an increased market understanding. Finally, the fourth strategy is to have insights in the competitive landscape (B4, B6), specifically referring to what competitors there are and what products they are developing.

Following this, the sixth barrier is a combination of the actor 'HTA agencies' and the factor 'market access criteria', which forms a barrier for developing the right product. The reason this is a barrier is because it is critical that a biopharma firms is aware of the country-relevant market access criteria from the HTA agencies for evaluating the product before launch (V3, V5, B4). The strategy to solve this is to bring in relevant experts on day 1 (V4),

meaning that the biopharma firm needs to find out and understand these criteria early by the support of relevant experts.

The seventh barrier is the skills 'self-awareness and self-criticism' because these skills are needed to understand where the real potential with the technology lies (V2, B8). If a firm has these skills, it will be more likely to make difficult decision about e.g. stopping the product development and head in another direction (B5, B6). The two suggested strategies to deal with this barrier are to be forward-looking in the approach (B3), and to go for the most difficult questions first (V2). The forward-looking mindset forces the firm to critically evaluate the current progress and see if it is in the right direction, and facing the most difficult questions first is smart to be able to stop a certain project in time if needed.

Finally, the last barrier is the combination of the actor 'policymakers' and the factor 'regulations' that together create a blockage. This is a barrier because the regulations in the field are getting increasingly stricter (B5), which can slow down and hamper innovative drug development (Hudson and Khazragui 2013). A biopharma firm needs to adapt its product development fit with the regulatory requirements from policymakers (Frederickson 2012). The policymakers can impact what products are beneficial to create by allocating their spending on certain disease prevention (B4). In order to deal with this barrier, the proposed strategy is to adapt the product to fit with current regulations (B6).

Goal 2: Find sufficient funding

The second goal in the valley of death is to find sufficient funding, where the sub model for this goal is shown in figure 6-9. The valley of death is a very capital-intensive phase for companies, making it crucial to have sufficient funding to be able to continue with the development all the way until market launch. The results of this thesis provided one facilitator and five different barriers that are influencing this goal. The respective strategies for dealing with these barriers will also be described here.

The facilitator that was identified for goal 2 is to have a good 'network around the company'. If a company has built a network with many different stakeholders in it, it can facilitate the process of finding the right stakeholders that have an interest to invest in a specific project or the company itself (B5, B6).

However, there were also five different barriers that seem to be blocking the goal of finding sufficient funding. The first one is the skills 'professionalism and business sense' (V2, B2, B8), which is a requirement to know how to handle external stakeholders (B2). There should be someone internally in the firm that possesses these skills when reaching out externally, e.g. a strong CEO (B1). Being professional and having business sense means knowing how to represent the firm to the outside world and what information to share (V2). The suggested strategy to solve this barrier is to have a strong person internally that can reach out and communicate with investors (V1, V2, B1).

Secondly, the skills 'communication skills' are also a barrier in this goal. In order to convince an investor to join the project, the person reaching out must be a good communicator to get the investors on board (B8). The strategy here is the same as for the previous barrier: have a strong person internally that can reach out and communicate with investors (V1, V2, B1).

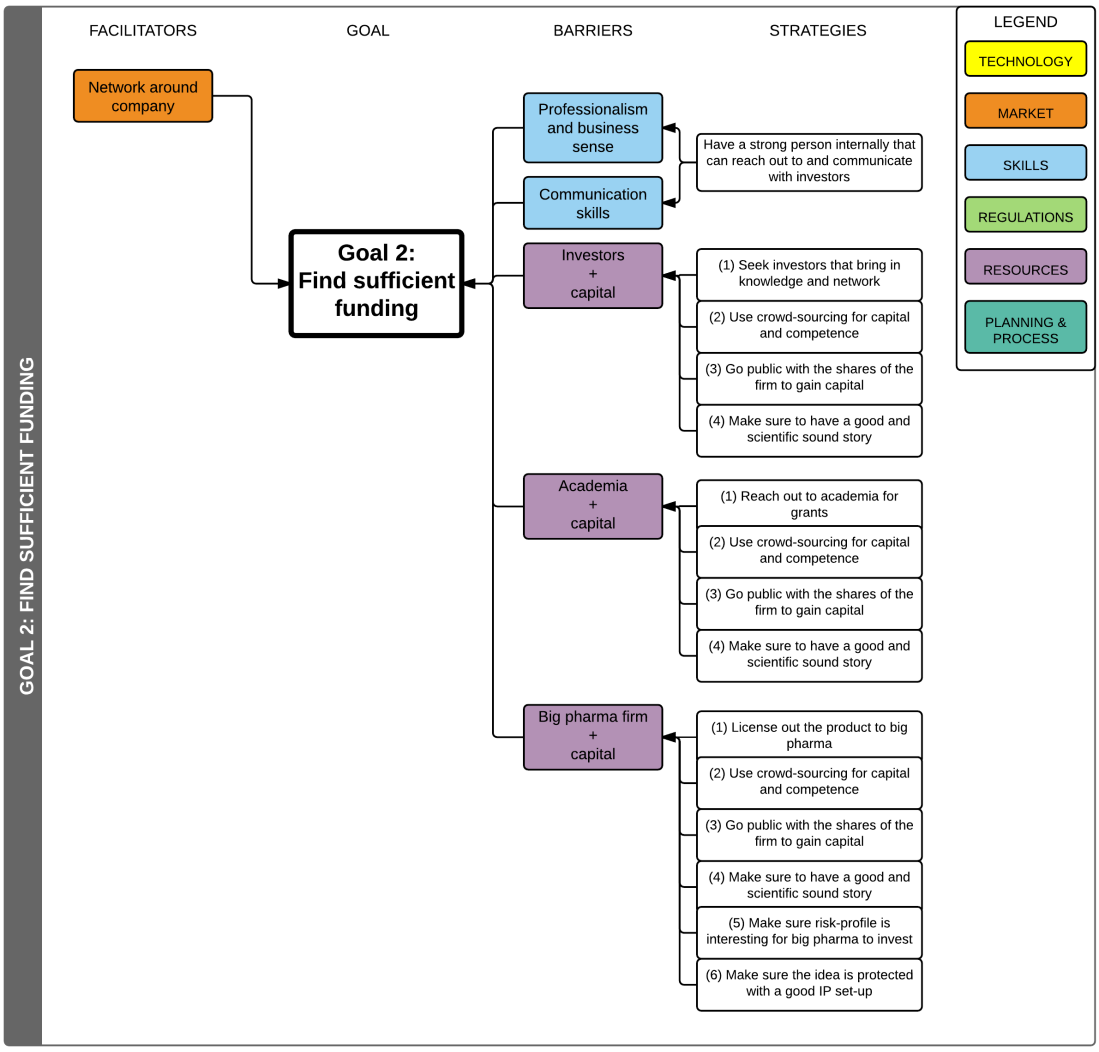

Figure 6-9: Goal 2: Find sufficient funding

The third barrier is a combination of the actor 'investors' and the factor 'access to capital' that together creates a barrier towards the goal if good investors with capital are lacking. The biopharma firm needs to have access to capital during the whole valley of death, which usually requires reaching out to external investors (B2, B3, B5, B6, (Frankel 2012), Frank, Sink et al. (1996)), e.g. venture capitalists of private equity companies (V1, V2, V5). There are four proposed strategies to deal with this barrier. The first one is to seek investors that bring in knowledge and network (V2, B6), which is a smart addition for a biopharma firm that usually needs more knowledge and competence during the difficult drug development process. The second strategy is to use crowdsourcing for capital and competence (Girdauskiene, Venckuviene et al. 2015). Crowdsourcing is a way to reach out to private investors, even normal persons that are interested in investing and also bringing in relevant knowledge to the project. Following this, the third strategy is to go public with the shares of the firm to gain capital (B2), which is a financial measure to raise more capital. Finally, if reaching out to investors,

the fourth strategy is to make sure to have a good and scientific sound story (B2, B6), since the investors need to be convinced that the scientific basis of the idea is good enough to bring sufficient return on the investment.

The fourth barrier is the combination of the actor 'academia' and 'access to capital', that together can be a barrier if they do not want to bring capital to the project. It is an option for a biopharma firm to reach out to academia in order to try and obtain grants as another way to find funding (V2). To tackle this potential barrier, there were four strategy suggestions described, where three of them are the same as the last three strategies for the previous barrier. They will therefore not be repeated again. The fourth strategy to tackle this is to reach out to academia for grants (V2), which is not always common for biopharma firms to do even though it presents a great opportunity to find funding.

Finally, the fifth barrier is also a combination, but this time with the actor 'big pharma firm' and the factor 'access to capital' that together creates a barrier towards finding sufficient funding. A biopharma firm can reach out to a big pharma firm to get capital, but at the same time get support on e.g. carrying out clinical trials (V1, V5). Due to the complexity of the clinical phase, it can be smart to use the experience of a big pharma firm for the execution, where one scenario is that the biopharma firm gets acquired by the big pharma firm. Through this, the big pharma can access an innovative product or idea, and the biopharma firm can continue its journey by being part of the large organization (B1). Of course, acquisition does not need to occur; a biopharma firm can also create a contract for partnership in order to get capital (B5). There are six different strategy suggestions to deal with this barrier, where three of them are the same as for the two previous barriers and will therefore not be explained further. The fourth strategy is to license out the product to big pharma (B5), which is a way to get funding without being acquired. The fifth strategy is to make sure the risk profile is interesting for big pharma to invest (V5). Finally, the sixth strategy is to make sure the idea is protected with a good IP set-up (B5), since big pharma firms are interested in protected ideas to secure exclusivity on future revenue streams.

Goal 3: Right skills and resources at right time

The third sub model is created for the goal to have the right skills and resources at the right time in the valley of death. Due to the long time period and many activities taking place, the need for certain skills and resources changes over time, forcing the company to adapt to this. For this goal, there were two facilitators identified, and four barriers with suggested strategy options. An overview of the sub model for goal 3 is presented in figure 6-10.

The first facilitator for reaching this goal is to have a good 'entrepreneur' with 'relationship management skills'. An entrepreneur can focus on building and maintaining external relations by the use of relationship management skills (V5, B6). Moreover, the entrepreneur could potentially help finding talented candidates that could benefit the firm (B8).

The second facilitator is 'support resources', which can have a positive influence on reaching goal 3 (B3, V5). Support resources can be e.g. business advice (V5), or academic incubators providing knowledge and advice (Bessiere, Gomez-Breysse et al. 2014).

Furthermore, the first barrier towards having the right skills and resources at the right time is the lack of a good 'network around company'. The reason that this is a barrier is be-

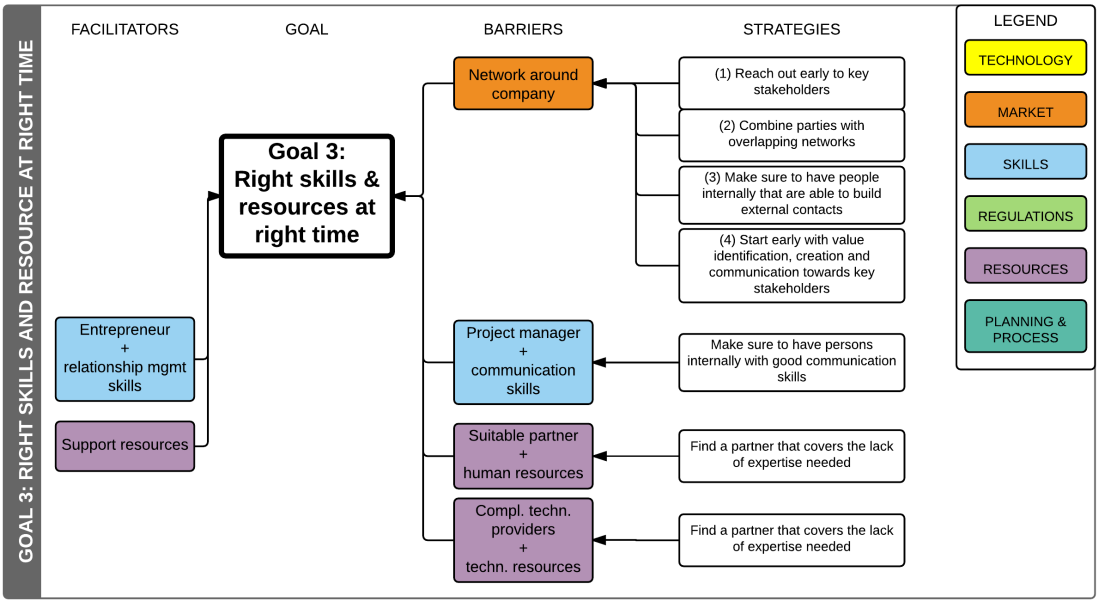

Figure 6-10: Goal 3: Right skills & resources at right time

cause lacking a good network seriously hampers the process to find the right skills and resources (V4, V5). A strong network can provide flexibility to a biopharma firm, in case another path seems more promising for the development process and therefore other skills are needed (V4). Having a good network means that a biopharma firm can get advice or find a suitable partner to work with, since it is almost impossible for a biopharma firm to travel alone through the valley of death (B8). For this barrier there were four different strategy suggestions. The first one is to reach out early to key stakeholders (V2, V3), in order to see whether critical skills and resources can be obtained early on. The second strategy option is to combine parties with overlapping networks (V4), because it is a way to further strengthen the external relations and increase the chances to reach goal 3. Furthermore, the third strategy is to make sure to have people internally that are able to build external contacts (B8), which refers to the internal perspective of a biopharma firm. Finally, the fourth strategy is to start early with value identification, creation, and communication towards key stakeholders (B2). By doing this, a firm can make sure that the external key stakeholders get on board early on and that they realize the benefit to join the network of the biopharma firm.

The second barrier is the combination of the actor 'project manager' and the factor 'communication skills', which in combination forms a barrier if a firm is lacking these. In other words, it is very important internally that there is a good project manager that can oversee the whole process of reaching out to external partners (B3). Moreover, the project manager must possess good communication skills in order to align internal processes and communicate the need for specific skills and resources to the rest of the organization (V5). The suggested strategy to deal with this is another version of the final strategy from the previous barrier; to make sure to have a person internally with good communication skills (B8).

The third barrier is the combination between the actor 'suitable partner' and the factor 'human resources', since lacking this can act as a barrier for a company trying to find the

right skills and resources (V5, B6, B7, B8). It is usually required that a biopharma firm collaborates with a suitable partner to find missing skills or human resources (B4), or finding an industry partner for complementary expertise (Coller and Califf 2009). Human resources refers to the skills available in a company (Bessiere, Gomez-Breysse et al. 2014), and it can be necessary for a company to reach out to complement these already for early stage development (Hudson and Khazragui 2013). The proposed strategy to deal with this barrier is to find a partner that covers the lack of expertise needed (V5, B2, B5, B6).

Finally, the last barrier is the combination of the actor 'complementary technology providers' and the factor 'technological resources'. Together these two create a barrier in case they are missing for a biopharma firm. The term technological resources refers to resources for the R&D activities, pre-clinical testing, and clinical testing (Clark 2013). It is crucial that the biopharma firm reaches out to complementary technology providers to find technological resources for e.g. production support (B1, B6). In order to deal with this barrier, the same strategy as for the previous barrier was suggested: find a partner that covers the lack of expertise needed (V5, B2, B5, B6).

Goal 4: Make intellectual property set-up

The fourth sub model is created for the goal to make intellectual property set-up. For a biopharma firm, a lot of its value lies in its intellectual property, so it is a key goal to make a suitable set-up to protect it against competitors, or for agreeing on terms with a partner. For this goal, one facilitator and two barriers were identified, with some connected strategies per barrier as well. The overview of this sub model can be seen in figure 6-11.

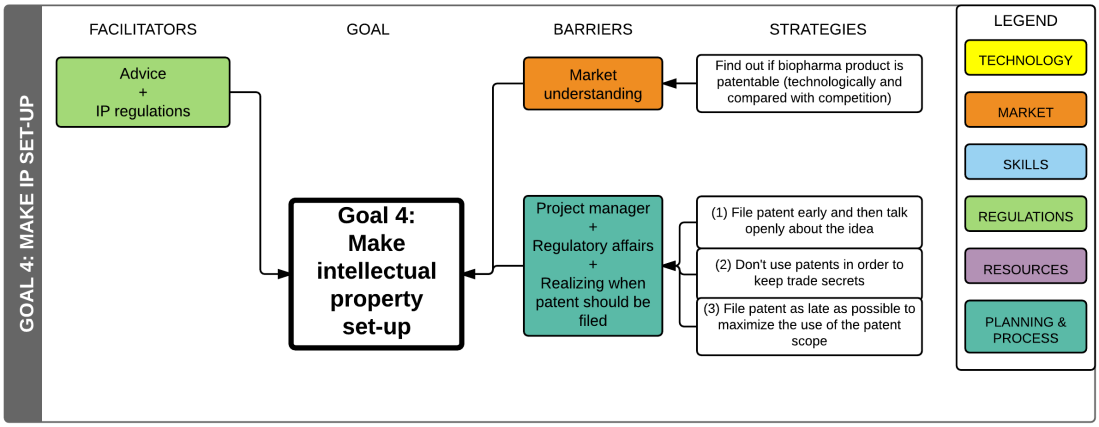

Figure 6-11: Goal 4: Make IP set-up

The first facilitator is the combination of the factor 'advice' and the factor 'IP regulations', that together can have a facilitating effect on reaching goal 4. It is good for a biopharma firm to get advice about IP regulations at an early stage, to avoid making beginner's mistakes (B6).

The first barrier is 'market understanding', which means that if a biopharma firm is lacking good market understanding, it can create a blockage for making a suitable IP set-up. More

specifically, a biopharma firm needs to know what is being developed in the market to understand what can be patented (B5). One strategy was proposed to deal with this barrier: find out if biopharma product is patentable (technologically and compared with competition) (B7). This is because an idea cannot be patented unless it has an inventive step, meaning that it offers something new towards competition. The nature of certain biopharma products make them not patentable, since it is not allowed by law to e.g. patent a normal human protein that every person has in their body.

The second and final barrier towards goal 4 is the combination of the actor 'project manager', the actor 'regulatory affairs', and the factor 'realizing when patent should be filed'. These two actors need to make a joint decision on when to file a patent, which is a critical decision, and therefore forms a barrier towards making a suitable IP set-up if it is not done in the right way (V1, V5, B2). The patent filing is a critical decision (B1, B8), especially because of the limited patent scope of 20 years (V1). The patent filing should preferably be done before the clinical phase (B3). In order to tackle this barrier, there are three strategies proposed. The first one is to file patent early and then talk openly about the idea (B5, B8), which is focused on protecting the idea towards other stakeholders. The second strategy is do not use patents in order to keep trade secrets (B1), where the approach is to not disclose any information and instead keep trade secrets and assume that the competitors cannot figure out how to copy the product. Finally, the third strategy is to file patent as late as possible to maximize the use of the patent scope (V5), which is a strategy focused on using the scope as much as possible. These three strategies cannot be combined, so it is a matter of preference for the company which one of them to use.

Goal 5: Plan and execute clinical trials

The fifth goal is to plan and execute clinical trials for the drug, which is a complex and expensive sub part of the valley of death. In figure 6-12, an overview of the created sub model for this goal can be seen. The model contains four different facilitators, and nine different barriers with suggested strategies to tackle them.

The first facilitator is the combination of the actor 'Key Opinion Leaders' and the factor 'advice', together having a facilitating effect to reach goal 5. A biopharma firm can reach out to KOLs to get advice, both on the design and execution of the clinical trials (V5, B4). Moreover, the KOLs can give advice on how to interpret the results from the trials (B1).

The second facilitator is the actor 'Contract Research Organizations', which can have a positive influence during the execution of the clinical trials. A biopharma firm can involve CROs to get support with the operational work or management of clinical trials (B3, B5, B6), and the CROs will then be the local contact for the physician carrying out the trials on the patients (B1).

The third facilitator is the combination of the actor 'Contract Manufacturing Organizations' and the factor 'manufacturing process', forming a facilitating effect on goal 5. CMOs can be involved to provide support with the manufacturing process for the drug that will be used in the clinical trials (B3, B5, B6).

Finally, the fourth barrier is the actor 'clinician-scientist', which is a medical doctor that is also pursuing scientific research. A clinician-scientist can be brought in to understand

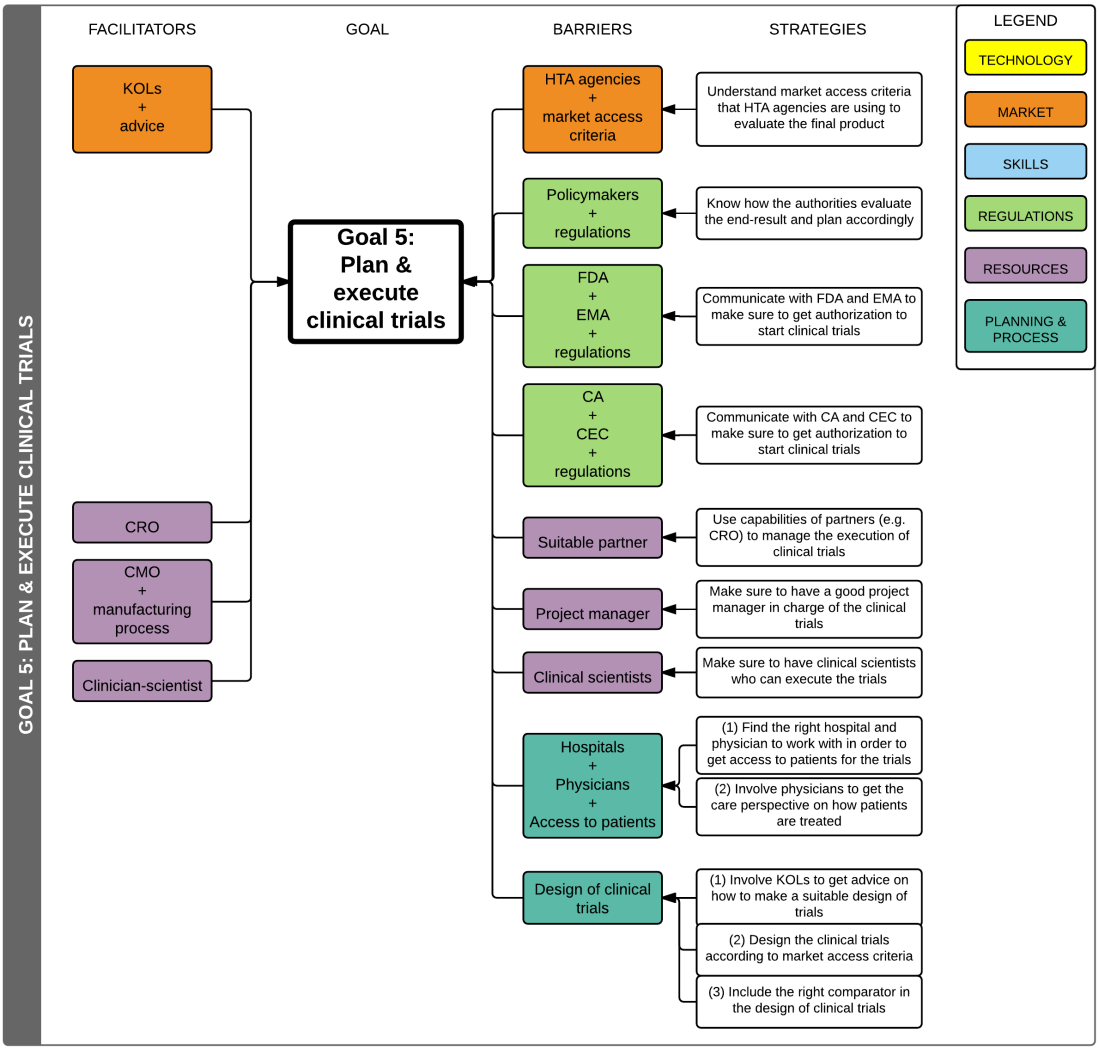

Figure 6-12: Goal 5: Plan & execute clinical trials

real-life situations regarding the patient care perspective, and can therefore have a positive influence on making successful clinical trials (V5). Moreover, clinician-scientists can give valuable insights regarding clinical applications (B6).

Furthermore, the first barrier is the combination of the actor 'Health Technology Assessment agencies' and the factor 'market access criteria', which in combination forms a barrier that biopharma firms need to deal with. It is crucial that a biopharma firm understands the country-relevant market access criteria, which are used by the HTA agencies to evaluate the final product before it is launched in the market (V3, V5). Thus, in order to plan and execute clinical trials, it is important that these criteria are understood and considered (V3, V5, B4). The proposed strategy to deal with this barrier is to understand market access criteria that HTA agencies use to evaluate the final product (V5).

Secondly, the next barrier is the combination of the actor 'policymakers' and the factor 'regulations', which together creates a barrier towards planning and executing clinical trials.

The reason for this is because the policymakers are setting the overall stage of what kind of products are beneficial to produce in the market, by allocating their spending towards certain disease areas (B4). The suggested strategy to tackle this is to know how the authorities evaluate the end-result and plan accordingly (B1). The end-result here refers to the final product that will be launched in the market.

The third barrier is a combination of the actor 'Food and Drug Administration', the actor 'European Medicines Agency', and the factor 'regulations', which in combination forms a barrier for goal 5 due to the fact that a biopharma must adapt to their regulations (V3, V5). A biopharma firm must get authorization from FDA and EMA to begin with the clinical trials (B3), and can also get continuous scientific and regulatory advice from them (B1). There is one suggested strategy for dealing with this barrier: communicate with FDA and EMA to make sure to get authorization to start clinical trials (B1, B2).

The fourth barrier is a combination of the actor ' Competent Authorities', the actor 'Central Ethics Committee', and the factor 'regulations', together creating a blockage for the biopharma firm when planning and executing the clinical trials. The CA and CEC are important to involve since they also have to provide an approval for biopharma firms to start the clinical trials (B2). They provide guidelines for clinical trials that a biopharma firm should follow (B2), including the ethical perspective on the drug development (B1). The proposed strategy is almost the same as for the previous barrier: communicate with CA and CEC to make sure to get authorization to start clinical trials (B1, B2).

Following this, the fifth barrier is the actor 'suitable partner', which can be a barrier since it is crucial that the firm finds good partners to work with to manage to get through the clinical phase (B7). The suggested strategy is to use capabilities of partners (e.g. CRO) to manage the execution of clinical trials (B6).

The sixth barrier is the actor 'project manager', which firms a barrier if this actor is not present within the biopharma firm. Overall, a project manager is needed to lead the execution and bring everything together during the clinical trials (B1, B4, B6). The proposed strategy is to make sure to have a good project manager in charge of the clinical trials (B4).

The seventh barrier is the actor 'clinical scientist', which is the actor that will do the actual clinical research work (V5), meaning that a lack of this actor will not make a successful clinical phase. The clinical scientists are crucial in order to do the operational work within the firm during the clinical trials (B3, B4). The strategy to solve this is to make sure to have clinical scientists who can execute the trials (B4).

The next barrier is the combination of the actor 'hospitals', the actor 'physicians' and the factor 'access to patients', that together are critical elements needed for a biopharma firm during the planning and execution of clinical trials. The biopharma firm needs to work with the right hospitals and physicians to get access to the patients to pursue the clinical testing on (V2, V5, B3). The hospitals and physicians are the ones carrying out all the work in the clinical testing (V5). There are two strategies proposed to deal with this: find the right hospital and physician to work with in order to get access to patients for the trials (B3), and involve physicians to get the care perspective on how patients are treated (B2, B4).

Finally, the last barrier is the factor 'design of clinical trials', which can form a barrier if a suitable design is not made. In order to carry out clinical trials, it is crucial to have a good design including a clinically relevant end-point to focus the development on (B2, Adams

(2012)), and including various expertise when making the design (Roberts, Fischhoff et al. 2012). The design should be made considering the relevant market access criteria, and should tie all components together in a final plan (V5). If the design is made in the wrong way, it can lead to failure during the trials that can be fatal for a biopharma firm (B3). In order to deal with this barrier, there were three strategies proposed. The first one is to involve KOLs to get advice on how to make a suitable design of trials (B2), since advice from KOLs can have a positive influence on the design. The second strategy is to design the clinical trials according to market access criteria (V5), which was mentioned as a previous barrier to plan and execute clinical trials. Finally, the last strategy is include the right comparator in the design of clinical trials (V3), which refers to how to show the effectiveness compared to something else.

Goal 6: Increase product development speed

Finally, the sixth goal is presented in figure 6-13. This goal is to increase product development speed in the valley of death, since it currently takes between 10 to 15 years to complete the phase. It also lies within a company's interest to be first to market, as being first to target a certain disease is very beneficial in the biopharma industry (B6). Moreover, if a company has a patent filed it is also crucial to get fast to the market to make use of the limited patent scope (V3). In order to achieve goal 6, the factors 'commitment' and 'information technology' are facilitators since they both positively influence the chances of reaching the goal

The first facilitator 'commitment' refers to a skill, or mind-set, that helps the company get through the long and expensive valley of death since it brings focus towards the end goal of getting a product in the market (B6), (Coller and Califf 2009). There will be a lot of moments filled with desperation in this development phase, and having commitment helps the company get through in a faster way and keeping up the good work (B8).

The second facilitator towards the goal is 'Information Technology ', which can offer the biopharma firm less complicated and faster ways to process all data gathered during e.g. clinical trials or screening (Rai, Reichman et al. 2008). Since the trials of today are very data-driven, having good IT solutions are very important to be able to increase the development speed (B2). In other words, IT is an internal resource that can really contribute to run the company in a better way through the valley of death (B1).

There are five different barriers that seem to be blocking the achievement of goal 6, but all these barriers can be tackled by the use of certain strategies.

The first barrier is 'clinical & market supply', because a lack of sufficient supply of the drug for both the clinical trials and for launching it in the market forms a barrier towards increasing the product development speed (B3). Producing a biopharma product is done within living systems, and it is crucial to make sure the drug can be produced at enough quantities to cover for the demand in the clinical trials as well as for the patients in the market when the drug is approved (B3). In order to deal with this barrier, the suggested strategy is to make sure to have a plan for the manufacturing to get sufficient supply to cover for the demands (B3).

The second barrier is 'regulations', since a biopharma firm needs to follow the strict regulations in the field for developing a drug (B2). Due to this, it could mean a delay for a firm during the product development because of all the checks of the product from a regulatory

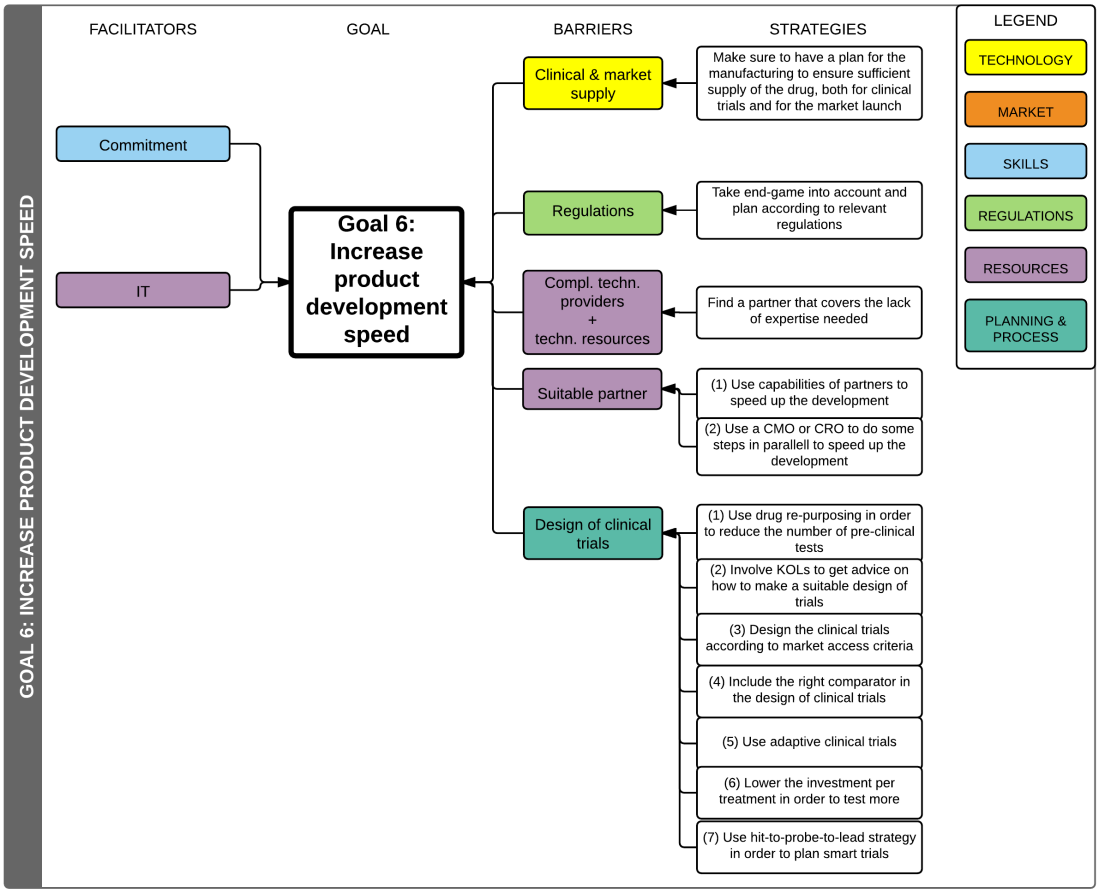

Figure 6-13: Goal 6: Increase product development speed

perspective (B2). For a small biopharma firm it is common that extensive knowledge about regulations is missing, which is why the regulations create a barrier towards goal 6 (B6). In order to deal with this barrier, the proposed strategy is to take the end game into account and plan according to relevant regulations (B2). The end game refers to the final goal of the product in the market, and to make sure that the product matches the regulations.

The third barrier towards goal 6 consists of a combination of the actor 'complementary technology providers' and the factor 'technological resources' that in combination forms the barrier. In other words, lacking technological resources from these providers can hamper the speed of product development (V5). It is not smart for a firm to "try to reinvent the wheel", as mentioned in one interview, but rather reach out to complementary technology providers for those resources (B6). A proposed strategy to deal with this barrier is to find a partner that covers the lack of expertise needed (B2, B5, B6, V5).

The fourth barrier is 'suitable partner', which is quite a broad term representing the need for a biopharma firm to find suitable partners to work with at different stages during the valley of death. A biopharma firm needs to realize what skills and resources are needed to be able to speed up the development, meaning that lack of a suitable partner can slow the firm down (B2, B6). There are two suggested strategies to deal with this barrier: use capabilities of

partners to speed up the development (V5), and use a CMO or CRO to do some steps in parallel to speed up the development (B2). The second strategy is also about partners, but refers in this case specifically to partners for the clinical work since this is a time-consuming part of the valley of death.

Finally, the fifth barrier is 'design of clinical trials', because this is a factor where a biopharma firm really can make a difference in the speed of the product development (V5). If the firm makes good choices on how to carry out the research, it might prevent delays (V5). All processes should be performed at the highest possible speed, and a good clinical trials design is crucial to make that happen (B6). In order to tackle this barrier, the different research methods provided seven different strategies: (1) use drug re-purposing to reduce the number of pre-clinical tests (Sem 2014), (2) involve KOLs to get advice on how to make a suitable design of clinical trials (B1, B2, B4), (3) design the clinical trials according to market access criteria (V5), (4) include the right comparator in the design of the clinical trials (V3), (5) use adaptive clinical trials to speed up (B3), (6) lower the investment per treatment in order to test more and get faster to market (B3), and (7) use hit to-probe-to-lead strategy in order to plan smart trials (Roy, Taylor et al. 2009).

Case example

An example to show the potential interrelations between choosing a strategy for one barrier within one goal and at the same time choosing a strategy for another barrier within another goal will now be described in terms of one of the biopharma companies. More specifically, this will illustrate how a fictive manager from company 2 could potentially select different strategies for different barriers.

In the first row in table 6-2, the list of the four suggested strategies for the barrier 'market understanding' from goal 1 is presented. In this fictive case, the manager is market oriented and chooses to use a combination of strategy 1, 3 and 4 to gain a better market understanding. For goal 2, the manager chooses the first strategy, since the combination of an investor that also brings in knowledge and network can positively influence the barrier to a good market understanding from goal 1. This is therefore a reinforcing combination of strategies. Finally, for goal 3 the manager chooses to use strategy 1 and 2 to deal with the barrier 'network around company'. These two strategies are not only contributing to tackle the barrier, but also positively reinforce the chosen strategies for goal 1 and 2. More specifically, the second strategy suggests combining parties with overlapping networks, which also help to get a better market understanding and find a suitable investor. The first strategy is about reaching out early to key stakeholders, which complements the other strategies by focusing on the timing of the contact. This small case example shows that the choices of strategies in different goals for different barriers can influence each other. In this case, the selected strategies positively reinforce each other. However, in order to be sure how other combinations of strategies can be done, the managers in the companies should do a similar check before taking the decisions. In general, the strategies are quite specific for a certain actor, factor or combination of the two, meaning that there should not be many situations with negative reinforcements.

In order to check for potential interference between barriers/facilitator for one goal towards another goal, they were checked and compared. The result can be seen in table 6-3, where the blue cells highlight interferences. If there was a barrier or facilitator that appeared in

Table 6-2: Illustrative case example about strategy interrelations

	Barrier	**Strategies**
Goal 1	Market understanding	**(1)** Be forward looking in the approach, (2) Communicate between company departments, **(3)** Understand the patient needs to see where to add value, **(4)** Have insights in the competitive landscape
Goal 2	Investors + capital	**(1)** Seek investors that bring in knowledge & network, (2) Use crowd-sourcing for capital and competence, (3) Go public with the shares of the firm to gain capital, (4) Make sure to have a good and scientific sound story
Goal 3	Network around company	**(1)** Reach out early to key stakeholders, **(2)** Combine parties with overlapping networks, (3) Make sure to have people internally (4) Start early with value identification, creation and communication towards key stakeholders

both compared goals, it was mentioned in the matrix. This information can be relevant for a manager to take into account when making an overall plan on how to solve all the six goals. For example, if an actor is a barrier in two goals at the same time, it can be smart to consider the strategy options to deal with both goals at the same time. If it says “no interference” in a box, it means that there are no facilitators or barriers in common for those two compared goals.

Table 6-3: Matrix showing comparisons between barriers and facilitators over the different goals

	Goal 1: Develop the right product	**Goal 2**: Find sufficient funding	**Goal 3**: Right skills & resources at right time	**Goal 4**: Make IP set-up	**Goal 5**: Plan & execute clinical trials	**Goal 6**: Increase product development speed
Goal 1	-	No interference	In both goal 1 and 3, project manager is a barrier	In both goal 1 and 4, market understanding is a barrier	In both goal 1 and 5, project manager and policymakers + regulations are barriers	In both goal 1 and 6, regulations is a barrier
Goal 2	No interference	-	In goal 2, network around company is a facilitator, but in goal 3 a barrier	No interference	No interference	No interference
Goal 3	In both goal 1 and 3, project manager is a barrier	In goal 2, network around company is a facilitator, but in goal 3 a barrier	-	No interference	In both goal 3 and 5, project manager and suitable partner are barriers	In both goal 3 and 6, suitable partner is a barrier
Goal 4	In both goal 1 and 4, market understanding is a barrier	No interference	No interference	-	No interference	No interference
Goal 5	In both goal 1 and 5, project manager and policymakers + regulations are barriers	No interference	In both goal 3 and 5, project manager and suitable partner are barriers	No interference	-	In both goal 5 and 6, regulations, design of clinical trials, and suitable partner are barriers
Goal 6	In both goal 1 and 6, regulations is a barrier	No interference	In both goal 3 and 6, suitable partner is a barrier	No interference	In both goal 5 & 6, regulations, design of clinical trials, and suitable partner are barriers	-

Chapter 7

Conclusion & Discussion

The following chapter is the final chapter of this thesis report, where the aim is to conclude and discuss further around the findings of the project. Section 7-1 will conclude if the objectives of the thesis are met, and why the different sub questions can provide a good answer to the main research question. In section 7-2, the societal and managerial impact will be explained, in terms of general societal relevance, managerial impact for biopharma firms, and finally business impact for Vintura. The next section, 7-3, will elaborate on the theoretical impact of the thesis in terms of impact on current literature, comparisons with similar literature, additions to the evolutionary innovation model, and comparisons of the created model with the niche strategy selection model. In section 7-4, the limitations of the thesis projects are described, regarding limitations on the generalization of the thesis results. Following this, section 7-5 contains the reflections on the choices made within this thesis. Finally, section 7-6 discusses about the research set-up and analysis, around the generalizability of the results, about a middle ground in the thesis model, about new ideas that arose during the thesis project, and about recommendations on future research possibilities.

7-1 Conclusions

In order to find an answer to the main research question, four different sub questions were formulated that together could be combined to find an answer to the main question. The main question is as follows *"What are key actors, factors and strategies that impact how biopharma companies move a radically new product from invention to a first market introduction?"* Moreover, some objectives were stated in the thesis, and the second paragraph in this section will describe whether and how they were achieved.

To be able to answer the main question, it was first necessary to get a better idea on what the valley of death looks like, in terms of time frame and main activities and goals for the companies. The first sub question provided a good answer to this by stating the time frame to be 10 to 15 years and identified six main goals that the company should aim for during this phase. The second sub question generated an answer regarding what the key actors and

factors are in this phase, and also how they relate to the main goals. Following this, the third sub question focused on understanding the interconnections between these actors and factors, which was an important part of the main question. Finally, the fourth sub question investigated the use of strategies in order to deal with the valley of death, and more specifically with each goal in the valley of death. These consolidated answers to all sub questions can be found in section 6-2. All together it can be concluded that using these four sub questions has provided a good answer to the main question, which can all be summarized in the created model in section 6-3.

In the beginning of this thesis report, there were five objectives stated in section 1-4. The first objective was *"to understand the phase known as the valley of death, and which actors and factors are involved there"*. This thesis project has contributed to achieve this objective through an increased understanding of the valley of death and its actors and factors. The second objective was *"to understand how these actors and factors are interconnected within this phase"*, where the created sub models in figure 6-8 to 6-13 are a good way to show the various interconnections. Following this, the third objective was *"to define and/or develop strategies for companies, that are commercializing radically new innovations, to deal with this phase"*, which has also been achieved since these strategies are also incorporated in the model. The fourth objective was *"to contribute to the understanding of the biopharmaceutical industry regarding the valley of death"*. This objective has also been achieved since the findings positively contribute to an increased understanding of how biopharma firms experience the valley of death. Finally, the last objective was *"to contribute with knowledge that can be used within the business of Vintura"*. The created model offers a practical tool for Vintura to use further in their advisory services towards clients in the biopharma field. In section 7-2 it will be further explained why this objective has been reached.

7-2 Societal and managerial impact

General societal relevance

The results from this thesis project contribute with a combination of theory and practice, making the results valuable for the players in the biopharma industry. The valley of death is a tough phase where many companies struggle with getting an innovative idea all the way from the point of invention until a market launch. From a holistic perspective, it affects not only the firms themselves but also the patients that cannot get access to all the innovations that die along the valley of death. Moreover, the costs of bringing a drug to the market are huge, resulting in really extensive losses in case a drug does not make it to the market, especially if the failure happens in the clinical phase. Through this thesis project, the understanding of the valley of death has increased. This could lead to more successful companies traveling in the valley of death and launching innovative drugs to tackle the medical challenges in the current society, which is why the findings are important from a societal point of view. With a population that is getting older, diseases such as Alzheimer's or various forms of cancer will become more common, and thus requires more efficient drugs to be treated. Therefore it is crucial to understand how the valley of death can be faced and overcome, to launch more innovative products in the market.

Managers in biopharma firms

The created model with the six goals in the valley of death has an impact for the managers or other decision-makers in the biopharma firms. The model is a combination of theory and practical suggestions, and offers hands-on solutions to make smart choices in the valley of death. Until this point there has been no overview of the challenges in the valley of death, and especially not on a visual display including causal relationships. From a managerial perspective, the created model is therefore beneficial since it is easy to follow and visualizes the most critical relationships in the valley of death. Furthermore, managers do seldom have time to go through large theoretical academic publications in order to solve their problems. By using this model, the managers can get a quick overview of the most critical elements in the valley of death and not lose too much time on going through a long written report.

The business impact for Vintura

The findings in this thesis can also positively influence the business of Vintura and their consultancy practices by offering an overview of the most critical goals that biopharma firms should aim to achieve to increase the success rate in the valley of death. Vintura works with a combination of theory and practice to offer solutions to their customer's main problems with their business. As mentioned, the practical model is easy to understand and offers concrete strategy suggestions to tackle the main issues. This knowledge can be used by Vintura when working with a client that is struggling during the creation of a new innovative product. Moreover, the model is a relevant topic of conversation to use when reaching out to new potential clients. Through this, Vintura can present that they have pursued academic research on the challenges in the valley of death in order to attract attention from new clients. An academic research project can further strengthen the credibility of Vintura and their work, thus providing an overall positive influence on their business activities.

7-3 Theoretical impact

Impact on the current literature about the valley of death

The results of this thesis research have added to the current literature about the valley of death. The results provide an overview of key actors and factors and their interconnections in the valley of death, which the current literature could not present. The literature identified mainly financial shortage to be a reason that there is a valley of death, while the findings from the thesis provide several other relevant perspectives that have an impact, e.g. regarding skills, resources, and speed of development. The list of key actors and factors in the valley of death from the literature has also been extended, since the other research methods could add many more important actors and factors. The relationships between these have also been more closely studied in this thesis, including what actors and factors are involved per goal in the valley of death. The literature did present some strategies, however the overall thesis results provide a much more extensive strategy selection with a more practical approach for the companies to use.

Moreover, the definition for the valley of death in the literature was focused more on the gap between basic and clinical research, whereas the thesis results show that planning and executing clinical trials is a key goal for companies to be able to launch a product in the market. Therefore it is relevant to consider broadening the definition of the valley of death (as was done in this thesis), to also include the activities after start of clinical research. In other words, the thesis results have proven that the current definition of the valley of death in the literature is not completely true, since the challenges do not stop after the firm reaches the clinical phase.

Comparison with literature about similar topics

In order to put the thesis findings into its context, a set of three articles by Ellen Moors, Professor in Sustainable Innovation at Utrecht University, were selected for comparison. All of the three articles are connected in different ways to the topic in this thesis project, but providing different aspects.

The first article studies the transition towards a sustainable system of drug development (Moors, Cohen et al. 2014). The article focuses on identifying factors causing a systematic failure of developing new drugs, and suggests that reforms of the patent system and regulatory structures are needed in order to create a transition to a sustainable system of drug development. Moreover, a reform would lower the entry barriers for smaller companies and create more competition in the market that could spur innovation. Regulations in the drug development process are becoming stricter, and fewer innovations reach the market according to the authors, which are similar findings as in this thesis research. The article studies the pharma industry and its struggles, but more from a high-level perspective, looking at systems and forces such as regulations, IP regulations and organizational topics. This means that the findings from the thesis project contribute with a company perspective on the struggle to bring new drugs to the market. In other words, the findings from a biopharma company perspective in this thesis complements the article's focus on the system as a whole.

The second article describes using metaphors as a method to envision future emerging technologies, with a comparison of two different areas in the drug development process (Boon and Moors 2008). More specifically, the article focuses on the early stage of technology development where many uncertainties exist regarding the subsequent development process and the wishes from various stakeholders. Even though the focus is not on the valley of death as defined in this project, the findings of the article are related to the early struggles in the drug development process. The article highlights the importance of bringing in various actors and their perspectives when developing a drug, which is also emphasized in this thesis research. The results from the thesis can therefore contribute with the identified key actors, factors and strategies to deal with the valley of death, as a complement to the findings in the article. Using the metaphors and methods in the article could potentially help envision how future drugs can make it through the valley of death.

Finally, the third article identifies barrier and strategies towards a cleaner production in the base metal industry (Moors, Mulder et al. 2005). In this context, clear production solutions are seen as radical, which are not implemented enough. The article therefore focuses on understanding what barriers are blocking this development, and what strategies that can be used to tackle them. Three important barriers were identified in the study: cost of

investment, high risk to commit capital to an unproven technology, and the intertwinement of current production system. In order to deal with the barriers, three groups of strategies were proposed: firm-internal, inter-firm, and firm-external strategies. The article takes the technological innovation perspective, which is related to the topic in this thesis, however focused on another industry. There are similarities between the article and this thesis with regard to studying barriers and strategies for implementation of radically new technologies. However, the article groups both the barriers and the strategies on a higher level while in this thesis they are more specific. Perhaps the findings from both studies could be combined to have two-level perspective on barriers and strategies in one industry, with both high-level and more specificity.

Additions to the research on the evolutionary innovation model

The innovation phase in the evolutionary innovation model developed by Ortt and Schoormans (2004) was explored in this thesis project, with a focus on the biopharma sector. Before this thesis project, there had been limited research on understanding the details on the innovation phase regarding what actors and factors are relevant here, how they are interconnected, and how strategies can be used to get through the phase in the best way. The results of this thesis project have therefore contributed to getting a better understanding of the innovation phase. In the article by Ortt and Schoormans (2004), it is mentioned that organizations like research institutes and universities play a central role in the innovation phase, however the findings of this thesis shows that there are many more actors such as key opinion leaders, policymakers and health technology assessment agencies, that also play a major role here. Therefore, the results are broadening the number of key actors in this phase. Furthermore, academia has proved to have a major role in the development of new innovative ideas, which is also lying slightly outside the scope of the valley of death as used in the thesis project. Thus, academia might have an even larger impact in the phase before the innovation phase starts.

Overall, the findings of this exploratory research thesis have created a better picture of what happens in the innovation phase, with a focus on the biopharma industry. The next step is to see whether these findings also are applicable for other industries.

Comparisons with niche strategy model

The developed model for the valley of death in this thesis, see subsection 6-3-3, can be compared with the niche strategy selection model developed by Ortt, Kamp et al. (2015), to see what the similarities and differences are in the model design. The niche strategy selection model contains a set of core factors, a set of influencing factors and different strategy options. The core factors and influencing factors can be combined in different ways to create specific market situations, which results in barriers that needs to be tackled with the choice of a suitable niche strategy. These factors and strategies are summarized in two tables in appendix D.

The thesis model has some other components compared with the niche strategy model. The thesis model is goal-oriented and displays six main goals that should be achieved in the valley of death, and there is a sub model per goal that shows the specific relationships. For each sub model there are facilitators, which are positively contributing to the goal, and barriers,

which are blocking the goal. For each barrier there is a set of strategy suggestions to use in order to overcome the specific barrier. This means that the fact that the model is goal-oriented, and includes facilitators, are new features compared with the niche strategy model. The facilitators are of secondary importance compared with the barriers, but should still be considered in order to reach the goals. In the niche strategy model there are also two layers of factors, but the relation between them is influential factors towards core factors, which is not the same as the facilitator and barrier relation. This difference in the models could be investigated further in order to see if they can be combined or adapted to reinforce each other.

The model in this thesis project contains barriers and strategies, like the niche strategy selection model, but the barriers and strategies are much more detailed and specific in the thesis model. The following two paragraphs elaborates further on barriers and strategies, respectively.

As seen in the first table in appendix D, the niche strategy model contains six core factors and six influencing factors, which are all on a quite high level. These can be combined to represent different market situations, and can sometimes work as barriers towards successful implementation of new technologies. In the thesis findings, there are in total 29 factors and 24 actors identified within various categories. Thus, in comparison, the thesis findings are more detailed and specific. There is some overlap with the factors between the thesis findings and the niche strategy model, e.g. the actor 'complementary technology providers' and the factor 'technological resources' from the thesis correspond to the factor 'complementary products and services' from the niche strategy model. Another example is the factor 'support resources' and the actor 'investors' from the thesis, which correspond to the factor 'support and investments' in the niche strategy model. In general, the actors and factors from the thesis findings are more precise than the niche strategy model factors, but there is overlap to be seen.

For the strategies, the niche strategy article provides ten different niche strategies that can be considered for the introduction of a radically new product in a specific niche. The strategies in the thesis model are applied specifically to tackle a certain barrier for a specific sub goal in the valley of death. The thesis model offers the possibility to choose a combination of several strategies to tackle barriers standing in the way of a goal. This is different from the niche strategy model, where the idea is to choose one out of the ten suggested niche strategies. Of course, the thesis model and niche strategy model tackles different phases in the innovation process, so they cannot completely be compared but the context for each specific case needs to be considered.

To conclude, the model developed in this thesis is *goal-oriented* and contains the component *facilitator*, which brings two new additions to the niche strategy selection model. It is possible that these results can be incorporated into the niche strategy section model to develop it further.

7-4 Limitations of research methodology

This section describes some of the limitations of the research methodology used in the thesis. There were three different research methods combined in the thesis research; (1) systematic literature review, (2) Vintura interviews, and (3) company interviews with biopharma firms.

The results from the literature review were limited by the use of the specific search phrase "valley of death" in order to find a manageable set of articles to analyze. However, there are other literature streams within innovation management that analyzes the path to develop a new product that probably were excluded by the use of this search term. Examples of these streams would be "fuzzy front-end of innovation", and "new product development theories". By using such a specific search term as "valley of death", there is also a risk to exclude articles that address the same time period but does not name it the valley of death. These reasons can therefore explain some limitations regarding the way the systematic literature review was conducted for this thesis project.

The second research methodology was to carry out expert interviews within the organization of Vintura. Due to a time constraint, a total of five interviews could be carried out within the organization, where one of the interviewees belongs to the external network of Vintura. It was concluded that these persons could contribute with sufficient answers to cover the knowledge level of the topic around the valley of death within Vintura, but of course to be sure that the whole organization is represented, it would be good to make a second round of interviews to verify the first results. This was not done due to the limited time frame for the thesis. Moreover, there were some limitations in terms of the interview set-up, which was semi-structured with some fixed structure and some open questions. The set-up was made based on the research questions in this thesis, which already framed the interviewer that these are the key things to look for regarding the valley of death, which can be seen as a limitation to the methodology.

Finally, company interviews with biopharma firms were carried out through interviews with two persons from each company, with a total of four companies included. Having two candidates from each company provided the chance to check whether two interviewees from the same organization would provide similar answers. Ideally, it would have been even better to have more interviews within each organization to ensure the validity of the results, which is why this can be seen as a limitation on the methodology. The interviews were carried out in a semi-structured way combining open questions with fixed structure. The fixed structure consisted of cards with actors and factors, with information found previously in the thesis, which in a way could frame the interviewee to believe that these were the key actors and factors and hamper the process of letting them figure it out themselves. This is therefore a limitation to the methodology. The reason it was still chosen to use these cards was due to a time constraint per interview. By using the cards, there was more time available for the interactive questions about interconnections and strategies, areas where the literature was lacking a good answer.

7-5 Reflection about choices made

During the planning and execution of the thesis project, some choices were made regarding the scoping and delineation of the project. The research was of exploratory nature, making it logical to frame the research question to investigate around key actors, factors and strategies in the valley of death. The different sub questions were chosen to create a good combination of perspectives to have some structure in the exploratory research. Moreover, it was difficult to know from the beginning where the answers to these questions best could be found, which was the reason why the three different research methodologies all were included. For each

methodology, the same set of research questions were investigated, sometimes leading to repetition of results for the different methods. On the other hand, repetition of results also works as verification that the answers are relevant. Overall, it was a good choice to combine the methods to bring in different perspectives on the topic.

Initially, the idea was to focus on the biotechnology industry, but since the different branches within biotechnology can be very different, it was necessary to change the scope from biotech to biopharma. This was a good choice in order to dig deeper into the specific characteristics of the valley of death, but of course it impacts the generalizability of the results.

In addition, the author of this thesis wrote a self-reflection regarding the planning and execution of the thesis project, and about expectations and final results. This reflection can be found in appendix A.

7-6 Discussion

The discussion section consists of five subsections. The first subsection, 7-6-1, discusses around three topics in the research set-up and analysis. Secondly, subsection 7-6-2 discusses the potential generalizability of the results from this thesis by drawing parallels to other industry sectors. The next subsection, 7-6-3, discusses another version of the created model from subsection 6-3-2. Following this, subsection 7-6-4 will present new ideas discovered during the research that were not directly part of the thesis project, and finally subsection 7-6-5 will discuss future research possibilities related to this topic.

7-6-1 Discussion about research set-up and analysis

This subsection describes three topics in the research set-up and analysis regarding the choices made there, and discusses what that meant for the research and the outcomes.

Actors and factors split into six categories

The first topic is the six different categories that were used to split actors and factors in chapter 2 (table 2-2), chapter 3 (table 3-1), and chapter 5 (table 5-1, 5-3, 5-5 and 5-7). In order to further analyze all actors and factors identified during the research it was decided to use six categories to sort them: (1) technology, (2) skills, (3) resources, (4) planning & process, (5) market, and (6) regulations. In the text in subsection 2-2-2 it was shortly explained how these six categories are defined and how they are different. *Technology* is about things related to the technology/product itself, e.g. characteristics of the product; *skills* means different human capabilities, e.g. relationship management skills; *resources* represent various resources needed internally in the firm, e.g. human resources; *planning & process* refers to all internal operations in the firm, e.g. design of clinical trials; *market* is about the external actors and factors influencing the biopharma firm, e.g. KOLs; and *regulations* is obviously actors and factors involved in the regulatory environment.

These categories were created to sort the information from all the three research methods regarding actors and factors in the valley of death. The categories cover relevant areas from

a company perspective, in where to place key actors and factors. The categories are mutually exclusive and collectively exhaustive. In other words it means that there is no overlap between the categories, mutually exclusive, and that the categories cover all the options possible, collectively exhaustive. The reason that the categories are mutually exclusive is explained by how the categories are defined in the previous paragraph, and also in subsection 2-2-2. There are similarities between the categories skills and resources, however the first category really refers to human skills and capabilities whereas the second one is about persons, capital or technology. Therefore, they can be seen as two separate categories. Additionally, the categories market and regulations also might seem similar at a first glance. The biopharma industry is very much steered by regulations, and even if the actors and factors here also are part of the external market environment, it is easy to separate them into another category. By doing so, the regulatory actors and factors can be distinguished from the actors and factors in the market, which is why these are two separate categories. Finally, the categories resources and market can also be perceived as similar, but there is also a logical explanation for why these are apart. Resources refer to internally needed resources in a biopharma firm, which potentially could be accessed from an actor in the market. As an example, a biopharma firm can reach out to complementary technology providers to get technological resources. In this case, the biopharma firm reaches out to an actor in the market to get these resources that are needed internally, which is the explanation why these two categories can be separated. Overall, the categories are collectively exhaustive since all the actors and factors from the research could be divided over the six described categories.

Interactive interview set-up

The interview set-up used for the last Vintura interview, and for all the biopharma interviews might have steered the outcomes of the thesis research. The set-up was presented earlier in the report, in section 3-1 and 5-2. During these interviews, a semi-structured and interactive set-up was used and where the four sub questions for the thesis were used to create the structure. For the third sub question, cards with actors and factors were presented to each interviewee, containing findings from previous research methods. Using a semi-structured set-up like this could potentially have steered the outcomes of the interviewees, by framing them into thinking about the valley of death in a way that matches the thesis topic. Presenting the interviewees with the cards may in particular have framed them into thinking that these were the main actors and factors, and limited their creativity to come up with new actors and factors. This choice was made in order to save time, and spend that time on going into depth with interconnections and strategies instead, which were more scarcely described in the literature for example. Although the outcomes may have been biased, the author considers the choice of using the set-up to be a suitable way to tackle the most critical issues during time pressure.

Split between facilitators and barriers

The created model in subsection 6-3-3, with a detailed sub model for each of the six goals in the valley of death, includes a split between the so-called facilitators and barriers. As previously described, the barriers are the most critical elements for biopharma companies to tackle in the valley of death, and the facilitators are also important but less critical than

the barriers. The facilitators are positively influencing the chance of reaching the goals, and should therefore be considered. The split between facilitators and barriers was created on the basis of analyzing all the results and interpreting the information to find out what actors or factors or combination of these either help or block reaching a certain goal. During the execution of the three research methods it was seen in the results that some things were more emphasized than others, which made it a logical step to classify the information according to its importance. In general, both the facilitators and barriers are important, but the split was made to create some depth in the findings and separate the most critical ones from the second-order actors and factors. In that way, a more interesting model could be created and visualized in a clear way.

7-6-2 Generalizability of the results

First of all, the thesis is focused on the biopharmaceutical industry, which is already providing a limitation to generalize the results of the thesis towards several other industries. With that said, there are still ways in which the results can provide value to other industries. First of all, as described in the introduction chapter of the thesis, the production process of making a drug has similar steps for both biopharma and pharma firms. This means that pharma firms could potentially use the model as well, for understanding what to focus on in the valley of death. Although the pharma firms usually are huge in size, they are facing the same goals as a biopharma firm in the valley of death. The main difference is perhaps that big pharma firms are better equipped to reach these goals easier and in a faster way, but they might face other difficulties such as hierarchical structures or complex organizational structures. This might mean that some goals are less important for pharma firms, and perhaps some additional goals need to be added to make the model complete.

Secondly, some of the elements in the final model could also be applicable for other types of biotech firms, e.g. med-tech companies that are producing implants and other medical equipment that interacts with the human body. Although the regulations are not as strict as for biopharma, a med-tech company still needs different types of approvals and certifications for their products to be launched in the market, e.g. by checks from FDA. This means that all goals from the created model in the thesis could be important for a med-tech firm as well, with the exception of goal 5 regarding clinical trials, which are specific for making a drug. Further research is needed to confirm if this is applicable.

Finally, it is interesting to discuss whether the findings are applicable for firms in other high-tech industries that do not focus on products interacting with the human body. One example of another high-tech industry is the information technology sector. However, since the speed of development is completely different here, with technologies becoming obsolete in a fast pace, it is doubtful whether the findings can be beneficial here, and if a valley of death even exists here. Another example is environmental technologies, since the time frame for taking a new environmental technology to market also takes long. Of course, the specific actors and factors related to the drug development have to be excluded and exchanged for other industry-relevant actors and factors. Firms developing environmental technologies also needs to know whether they develop the right product, whether they have the right skills and resources at the right time, and needs to find sufficient funding and protect the ideas with IP. Of course, this has not been further investigated in this thesis project, but could be a potential industry to apply these thesis findings to.

7-6-3 Key elements of the model

The developed model in subsection 6-3-3, contains six main goals that ideally should be achieved by biopharma companies experiencing the valley of death. This subsection contains a short elaboration on the six categories used to classify all the information in each sub model: (1) technology, (2) market, (3) skills, (4) regulations, (5) resources, (6) planning & process. These are displayed by the various colors in the visualizations in subsection 6.3.3, and they are summarized in the legends in each figure.

In order to make sense of all the details in the sub models, the author tried to find a way to summarize and cluster the information from the sub models to simplify it. The result of this became the six categories used to classify all the information, which meant that the author came back to the same groupings again.

By using all of these six categories, it is possible to summarize where the main challenges for biopharma firms lie in the valley of death. Basically, if one wants to understand this phase it is possible to say that there are some issues for each of these six categories. However if more information is required, then it is possible to go into the details for each of the goals through the respective sub model. To summarize this means that the biopharma firms experience issues within the six categories technology, market, skills, regulations, resources and planning & process.

7-6-4 New ideas discovered during thesis

During this exploratory thesis research, some other interesting ideas were found that could not directly be linked to the specific research questions. There were three main topics discovered: (1) innovate new drugs, (2) small versus large firms in the valley of death, and (3) organizational structure of a company. Here follows a short explanation on the ideas.

Innovate new drugs

On several moments during the thesis research, the topic of innovating new drugs or create innovative ideas has been brought up. It almost seems as if the process of creating a new innovative idea can be a new valley of death on its own, due to its complexity and challenges. Earlier in this thesis it was explained that a pre-condition to enter the valley of death was to already have an innovative idea that can be developed further. This is the main reason that the process of how to find or create such an idea was excluded from the thesis research. However, in the literature as well as in the Vintura interviews and biopharma company interviews, it was brought up that creating an innovative new drug is a struggle. This sometimes involves the translation of an idea from basic to clinical science, and therefore includes a complex interplay between academia and industry to create a win-win situation and bring new scientific findings all the way to the patients. The innovative capacity of large pharma firms is getting more limited recently, which is one reason that many biotech companies get acquired by these large firms. This topic can therefore on its own create another valley of death regarding innovation, which companies first need to survive before entering the "real" valley of death. For these reasons, and since it is part of the "literature valley of death" as described in chapter 1, this could be interesting to study further.

Small versus large firms in the valley of death

Another topic that has been discovered during the thesis is whether there are any differences on how small and large firms experience the valley of death. It is still not clear if there are any major differences in how small and large firms deal with the valley of death. Of course, the most obvious thing is that a larger firm usually has more resources, capabilities and experiences. This also means that a larger firm is better prepared to deal with unexpected situations, and has some backup capital to rely on if needed. However, since biopharma firms are working as a network organization in many ways, it can bring in relevant expertise and knowledge by working with partners. Then it becomes hard to compare small versus large firms, since the small firms are not in this situation on their own anymore. It seems like both small and large firms want to achieve the same goals in the valley of death, but will have different starting levels regarding knowledge, resources and relevant experience. Just because a large firm is large does not mean it will survive the valley of death for sure, because tests can still fail in a late stage of the clinical trials, which is incredibly hard to recover from. To summarize, it was not yet clear after this thesis research whether small and large firms experience the valley of death in different ways, and if they do, what the differences are.

Organizational structure of a company

The last topic of new ideas from this thesis is about organizational structure of a company. It was indicated in the literature that the valley of death provides a change in roles within a company over time. In other words, the internal structure of a company might need to adapt to different characteristics of the sub parts of the valley of death. In one interview from Vintura it was also mentioned that an entrepreneur is important in the beginning, to advocate the idea to the outside world. In the next step, a manager became more important in order to create a focus and structure within a company. Therefore it can be interesting to find out more about how a company ideally should adapt the internal organization to fit with the dynamics of the valley of death.

7-6-5 Future research possibilities

This final subsection contains some recommendations for future research topics related to the thesis topic.

The first recommendation is to validate the created model with other biopharma firms. It would be interesting to see whether other firms in the same industry agrees with the model, and potential adaptions could be made to make sure that the key elements are correct. Doing in-depth interviews with a few different interviewees from different biopharma companies is a qualitative way to verify the model. Another option is to verify it in a more quantitative way, e.g. through a survey where the participants e.g. has to rate the accuracy of the model. Another way to verify the model is to let some biopharma companies use it in a fictive or real case, to see whether it makes sense in practice.

Secondly, the model can be adapted to fit with pharma firms, which requires including their views on the valley of death and the main challenges there. One way to do this is using company interviews in the same way as in this thesis, but with pharma firms instead.

Moreover, future research can focus on understanding the valley of death for other high-tech industries to see what key challenges companies experience there. Then it is also possible to use the model from this thesis and adapt the components and content to fit to a new industry. For example, the general structure of the model with goals, facilitators, barriers, and strategies can be kept, but the content can be filled with industry-relevant topics.

Following this, it could be interesting to change the perspective of how the study is made, e.g. change from company perspective to policymakers' perspective. There are many incentives for policymakers to understand the valley of death further and see how policy instruments could contribute to more successful transitions of ideas into products. This could be applicable for several fields where a valley of death exists.

Finally, research can be done in the three related areas just described in subsection 7-6-2, (1) innovate new drugs, (2) small versus large firms in the valley of death, and (3) organizational structure of a company, in order to add to the understanding of the valley of death and its surroundings from a company perspective.

Bibliography

Adams, D. J. (2012). "The Valley of Death in anticancer drug development: a reassessment." Trends in pharmacological sciences **33** (4): 173-180.

Beach, T. G. (2013). "Alzheimer's Disease and the "Valley of Death": Not Enough Guidance from Human Brain Tissue?" J Alzheimers Dis **33**(Suppl 1): S219-S233.

Bessiere, V., et al. (2014). "How Do Research-Based Start-Ups Overcome The Valley of Death?".

Boon, W. and E. Moors (2008). "Exploring emerging technologies using metaphorsÐa study of orphan drugs and pharmacogenomics." Social science & medicine **66**(9): 1915-1927.

Bruinsma, V. (2015). Developing a dynamic framework for the selection of niche strategies to introduce new high-tech products, TU Delft.

Butler, D. (2008). "Translational research: crossing the valley of death." Nature News **453**(7197): 840-842.

Carroll, S. (2009). "Goodbye blockbuster medicines; hello new pharmaceutical business models." Retrieved 2015-09-08, from http://www.pharmaceutical-journal.com/opinion/comment/goodbye-blockbuster-medicines-hello-new-pharmaceutical-business-models/10966185.article.

Clark, J. (2013). "5. Traversing the valley of death." Healthcare: Reform or ration: 67

Coller, B. S. and R. M. Califf (2009). "Traversing the valley of death: a guide to assessing prospects for translational success." Science translational medicine **1**(10): 10cm19-10cm19.

Denyer, D. and D. Tranfield (2009). "Producing a systematic review."
Disis, M. L. and J. T. Slattery (2010). "The road we must take: multidisciplinary team science." Science translational medicine **2**(22): 22cm29-22cm29.

Dorey, E. (2009). "Awards bridge'valley of death'." Nature Biotechnology **27**(8): 678-678.

Edwards, G. (2012). "VALLEY OF DEATH." Science in Parliament **69**(1): 34.

Eisenhardt, K. M. (1989). "Building theories from case study research." Academy of management review **14**(4): 532-550.

EMA (2016). Retrieved 2016-02-17, from $http://www.ema.europa.eu/ema/index.jsp?curl = pages/regulation/general/general_content_000029.jsp$.

Frank, C., et al. (1996). "Surviving the "valley of death": A comparative analysis." The Journal of Technology Transfer **21**(1-2): 61-69.

Frankel, P. (2012). "A helping hand: Part one: could a new type of insurance help cutting edge renewable energy companies cross the valley of death?" Renewable Energy Focus **13**(1): 46-49.

Frederickson, R. M. (2012). "Escaping the Valley of Death: The NIH Gene Therapy Symposium Bethesda, Maryland, USA 26Ð27 September 2011." Molecular Therapy **20**(3): 476.

Gans, J. and S. Stern (2004). "Managing Ideas: Commercialization Strategies for Biotechnology."

Gans, J. S. and S. Stern (2003). "The product market and the market for "ideas": commercialization strategies for technology entrepreneurs." Research Policy **32**(2): 333-350.

Girdauskiene, L., et al. (2015). "Crowdsourcing as a Key Method for StartÐups Overcoming Valley of Death." Mediterranean Journal of Social Sciences **6**(3): 795.

Guedj, I. and D. Scharfstein (2004). Organizational scope and investment: Evidence from the drug development strategies and performance of biopharmaceutical firms, National Bureau of Economic Research.

Hamburg, M. A. and F. S. Collins (2010). "The path to personalized medicine." New England Journal of Medicine **363**(4): 301-304.

Hudson, J. and H. F. Khazragui (2013). "Into the valley of death: research to innovation." Drug discovery today **18**(13): 610-613.

Khilji, S. E., et al. (2006). "From Invention to Innovation: Toward developing an integrated innovation model for biotech firms*." Journal of product innovation management **23**(6): 528-540.

Kotler, P. (1971). Marketing Decision Making: A model building approach.

Kotler, P. (1980). Principles of Marketing.

Markham, S. K. (2004). "Product champions: Crossing the valley of death." Belliveau P, Griffin A, Somermeyer SM the PDMA Toolbok for New Product Development: 119-140.

Markham, S. K., et al. (2010). "The valley of death as context for role theory in product innovation." Journal of product innovation management **27**(3): 402-417.

Mimura, C., et al. (2011). "Perspective: Socially Responsible Licensing, Euclidean Innovation, and the Valley of Death." Stanford Journal of Law, Science and Policy.

Moors, E. H., et al. (2014). "Towards a sustainable system of drug development." Drug discovery today **19**(11): 1711-1720.

Moors, E. H., et al. (2005). "Towards cleaner production: barriers and strategies in the base metals producing industry." Journal of Cleaner Production **13**(7): 657-668.

MorganMcKinley (2013). "Difference between Pharmaceutical and Biotechnology." Retrieved 2015-08-21, from http://www.morganmckinley.ie/article/difference-between-pharmaceutical-and-biotechnology.

Ortt, J.R., Kamp, L.M., Doe, M.F.A. (2015). Niche Strategy Selection to Introduce Radically New Systems; The case of kite-based airborne wind energy. Paper presented at the ICE Conference, 22-24 June 2015, Belfast, Northern Ireland.

Ortt, J. R. and J. P. Schoormans (2004). "The pattern of development and diffusion of breakthrough communication technologies." European Journal of Innovation Management **7**(4): 292-302.

Rai, A. K., et al. (2008). "Pathways across the valley of death: novel intellectual property strategies for accelerated drug discovery." Yale journal of health policy, law, and ethics **8**(1).

Reed, J. C. (2011). "NCATS could mitigate pharma valley of death."

Roberts, S. F., et al. (2012). "Perspective: transforming science into medicine: how clinicianÐscientists can build bridges across research's "valley of death"." Academic Medicine **87**(3): 266-270.

Roy, A., et al. (2009). "Hit-to-Probe-to-Lead Optimization Strategies: A Biology Perspective to Conquer the Valley of Death." Handbook of Drug Screening: 21-55.

Sabatier, V., et al. (2010). "From recipe to dinner: business model portfolios in the European biopharmaceutical industry." Long Range Planning **43**(2): 431-447.

Seibel, E. J. (2010). "Side-stepping the valley of death in New York City." Potentials, IEEE **29**(1): 14-18.

Sem, D. S. (2014). "Repurposing-Finding New Uses for Old (and Patented) Drugs: Bridging the Valley of Death to Translate Academic Research into New Medicines." Marq. Intell. Prop. L. Rev. **18**: 139.

Vintila, S. (2015). Sequences of Niche Strategies: An Exploratory Multiple-Case Study in Automotive, TU Delft.

Weston, A. D. and L. Hood (2004). "Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine." Journal of proteome research **3**(2): 179-196.

Williams, E. (2004). "Crossing the Valley of Death." Warwick Ventures, University of Warwick.

Wong, T. (2014). "How to bridge the'valley of death'between a research discovery and clinical application." Translational Medicine **43**(8).

Xia, T. and S. Roper (2008). "From capability to connectivityÑAbsorptive capacity and exploratory alliances in biopharmaceutical firms: A USÐEurope comparison." Technovation **28**(11): 776-785.

Appendix A

Self-reflection on thesis project

This appendix includes a short self-reflection from the author of this thesis report. I will discuss further around the project process, and provide a self-reflection on my own role in the project.

The thesis project has been very interesting to carry out, where I got the chance to combine my biotech background with my interest for management challenges in the commercialization process of new technologies. Due to the exploratory nature of the project, it was very good to combine the different research methods to find the answers to the questions. I personally like to have variation in my work, which is why I really liked to have a combination of methods. Of course, looking at the result of the thesis in terms of this report, it can be seen that it has been quite some work to carry out and combine all three methods. In other words, it feels like we have been quite ambitious in bringing all of these aspects into one thesis project. The process have been running smooth overall, and the planning and execution of all the interviews went well. It was great that Vintura could offer many valuable contacts internally and externally for both the Vintura and biopharma interviews. I am also very happy about the skills and writing skills I have improved by working with Vintura, and learning how to get a key message across. I feel that the communication between all stakeholders in this project have been good, and I have worked hard to keep everyone on the same page. I am very happy with the created model, as I struggled a bit with creating it at first. It is a very new experience for me to build such a model, and I can now look back to it and be proud what we have achieved. I could never have imagined that we could end up with a model like this, so I am very happy with the end-result.

Initially, my role in the project was smaller, since I needed guidance and support from all my supervisors to get into the work and head in the right direction. The research area I went into was quite new, which provided a challenge for me to work in an "empty space" and create my own structure. Over the process, I feel I have grown into my role as taking more of a project manager role and trying to keep all people in the project on the same page. From previous experiences in life, I know that communication is very important, so I tried my best to communicate key information between all stakeholders in the project. I have learned and grown in this project, and I hope my supervisors also have enjoyed working all together.

Appendix B

Overview actors and factors per goal in the valley of death

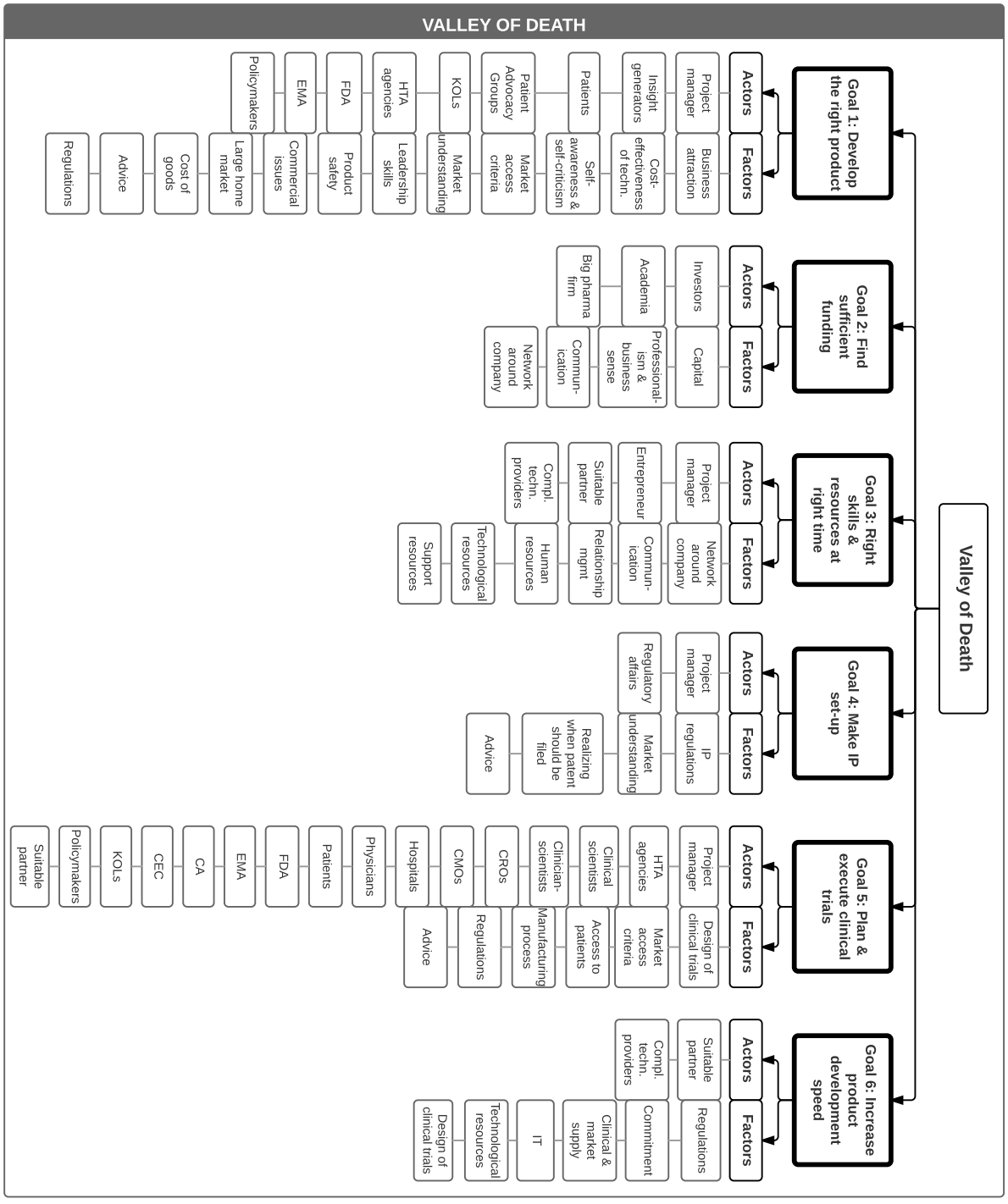

Figure B-1: Overview of actors and factors per goal in the valley of death

Appendix C

Key actors and factors from literature review

Table C-1: Actors and factors from company 1

Actor	Sources	Factor	Sources
Basic scientist	(Butler 2008), (Roberts, Fischhoff et al. 2012), (Coller and Califf 2009), (Beach 2013), (Reed 2011), (Wong 2014), (Clark 2013), (Sem 2014)	Innovative idea	(Coller and Califf 2009), (Markham, Ward et al. 2010), (Rai, Reichman et al. 2008), (Sem 2014)
Clinical scientist	(Butler 2008), (Roberts, Fischhoff et al. 2012), (Coller and Califf 2009), (Beach 2013), (Wong 2014), (Clark 2013),	Cost-effectiveness of technology	(Coller and Califf 2009), (Adams 2012), (Seibel 2010)
Clinician-scientist	(Wong 2014), (Clark 2013), (Roberts, Fischhoff et al. 2012), (Wong 2014)	Commercial issues	(Adams 2012), (Frank, Sink et al. 1996), (Hudson and Khazragui 2013)

Continued on next page

Table C-1 – continued from previous page

Actor	Sources	Factor	Sources
Entrepreneur	(Bessiere, Gomez-Breysse et al. 2014), (Frank, Sink et al. 1996)	Access to capital	(Edwards 2012), (Roberts, Fischhoff et al. 2012), (Adams 2012), (Frank, Sink et al. 1996), (Hudson and Khazragui 2013), (Clark 2013), (Frederickson 2012), (Bessiere, Gomez-Breysse et al. 2014), (Girdauskiene, Venckuviene et al. 2015), (Frankel 2012), (Rai, Reichman et al. 2008), (Sem 2014), (Dorey 2009)
Suitable partner	(Coller and Califf 2009), (Hudson and Khazragui 2013)	Leadership skills	(Girdauskiene, Venckuviene et al. 2015), (Frank, Sink et al. 1996)
Academia	(Rai, Reichman et al. 2008), (Hudson and Khazragui 2013), (Wong 2014), (Clark 2013), (Sem 2014), (Bessiere, Gomez-Breysse et al. 2014), (Seibel 2010)	Support resources	(Markham, Ward et al. 2010), (Coller and Califf 2009), (Adams 2012), (Markham 2004), (Clark 2013), (Bessiere, Gomez-Breysse et al. 2014)
Patients	(Clark 2013), (Wong 2014)	Communication	(Butler 2008), (Coller and Califf 2009), (Adams 2012), (Markham 2004), (Wong 2014)
Physician	(Roberts, Fischhoff et al. 2012), (Wong 2014)	Relevant knowledge & innovative capabilities	(Bessiere, Gomez-Breysse et al. 2014), (Butler 2008), (Clark 2013), (Edwards 2012)
Champions, sponsors, gatekeepers	(Markham, Ward et al. 2010), (Markham 2004), (Frank, Sink et al. 1996)	Right skills & resources at right time	(Clark 2013), (Coller and Califf 2009), (Hudson and Khazragui 2013), (Markham, Ward et al. 2010), (Wong 2014)
Food and Drug Administration, FDA (U.S.)	(Beach 2013), (Reed 2011), (Frederickson 2012), (Wong 2014), (Sem 2014)	Human resources	(Markham, Ward et al. 2010), (Coller and Califf 2009), (Adams 2012), (Markham 2004), (Clark 2013), (Bessiere, Gomez-Breysse et al. 2014), (Girdauskiene, Venckuviene et al. 2015)

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Table C-1 – continued from previous page

Actor	Sources	Factor	Sources
National Institute of Health, NIH (U.S.)	(Butler 2008), (Rai, Reichman et al. 2008), (Beach 2013), (Reed 2011), (Wong 2014), (Clark 2013), (Frederickson 2012), (Sem 2014)	Technological resources	(Markham, Ward et al. 2010), (Coller and Califf 2009), (Adams 2012), (Markham 2004), (Bessiere, Gomez-Breysse et al. 2014)
BioIndustry Association, BIA (UK)	(Edwards 2012)	Information technology, IT	(Girdauskiene, Venckuviene et al. 2015), (Rai, Reichman et al. 2008), (Frank, Sink et al. 1996)
Investors	(Frank, Sink et al. 1996), (Hudson and Khazragui 2013), (Reed 2011), (Dorey 2009), (Frankel 2012), (Edwards 2012), (Rai, Reichman et al. 2008)	Design of clinical trials	(Adams 2012), (Clark 2013), (Coller and Califf 2009), (Roberts, Fischhoff et al. 2012)
Policymakers (government)	(Coller and Califf 2009), (Hudson and Khazragui 2013), (Edwards 2012), (Wong 2014)	Commitment	(Coller and Califf 2009), (Frank, Sink et al. 1996)
		Intellectual property protection, IP	(Coller and Califf 2009), (Adams 2012), (Clark 2013), (Seibel 2010), (Rai, Reichman et al. 2008), (Sem 2014)
		Market understanding	(Coller and Califf 2009)
		Regulations	(Adams 2012), (Frank, Sink et al. 1996), (Hudson and Khazragui 2013), (Beach 2013), (Wong 2014), (Clark 2013), (Frederickson 2012), (Roberts, Fischhoff et al. 2012)

Appendix D

Factors and strategies from niche strategy model

Table D-1: Core and influencing factors from niche strategy model

Core factors	Influencing factors
New high tech product	Knowledge of technology
Production system	Knowledge of application
Complementary products and services	Natural resources and labor
Support and investments	Socio-cultural aspects
Customers	Macro-economic aspects
Institutional aspects (laws & rules)	Vision and image

Table D-2: Specific niche strategies and the descriptions of them

Strategies	Description of the specific niche strategy
1 Demo, experiment and develop niche strategy	A niche strategy can be adopted to demonstrate the product in public in a controlled way so the limited quality of performance is not a problem. As part of the strategy experimenting with the product is important to develop the product further.
2 Top niche strategy	A niche strategy can be adopted where hand-made products can be made to order, in small numbers, for a specific top-end niche of the market. A skimming strategy can be adopted in which the top niche of customers is supplied first with a special product.
3 Subsidized niche strategy	A niche strategy can be adopted where the product is subsidized if its use by a particular segment of users is considered societally relevant or important.
4 Redesign niche strategy	A niche strategy can be adopted where the product is introduced in a simpler version that can be produced with the existing knowledge, less use of resources and therefore for a lower price.
5 Dedicated system or stand-alone niche strategy	A niche strategy can be adopted where the product is used in stand-alone mode or a dedicated system of complementary products and services is designed (e.g. a local network when an infrastructure us not available on a wider scale).
6 Hybridization or adaptor niche strategy	A niche strategy can be adopted by which the new product is used in combination with the old product and thereby all existing complementary products and services can be re-used. Or an adaptor/convertor is provided to make the product compatible with existing complementary products and services.
7 Educate niche strategy	A niche strategy can be adopted aimed at transferring the knowledge to suppliers and customers.
8 Geographic niche strategy	A niche strategy can be adopted in another geographic area where the conditions are more favorable.
9 Lead user niche strategy	A niche strategy can be adopted finding innovators or lead users. These users can co-develop the product because they are willing to experiment with the product.
10 Explore multiple markets niche strategy	A niche strategy can be adopted in which multiple customer applications can be explored. Visibility of the first applications might stimulate explorative use in new applications.

Appendix E

Individual Ventura interviews

This appendix has been excluded from the public version of this thesis. Please contact the author for more information.

Appendix F

Individual Biopharma interviews

This appendix has been excluded from the public version of this thesis. Please contact the author for more information.