Market access for small ventures in the pharmaceutical industry

A study to explore the critical success factors for market access and to design a decision-support tool

Charlotte de Jonge
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Delft University of Technology

Chairman: Prof. Dr. Cees van Beers, Economics of Technology and Innovation, Technology Policy and Management, Delft University of Technology
First supervisor: Prof. Dr. Marina van Geenhuizen, Economics of Technology and Innovation, Technology Policy and Management, Delft University of Technology
Second supervisor: Dr. ir. Bauke Steenhuisen, Policy, Organization, Law & Gaming, Technology Policy and Management, Delft University of Technology
External supervisor: MSc. Sijme Zeilemaker, to-BBB technologies BV, Leiden

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EXECUTIVE SUMMARY

In the pharmaceutical industry, successful market access by small ventures has gained considerable attention in recent years due to transformations in the industry as a result of individualized value propositions, focus on delivering health outcomes and comprehension of the value drivers of new market stakeholders. For effective new product launches to meet revenue and profit expectations, pharmaceutical companies are facing large challenges to gain optimal market access, but also relatively large risks. These risks are particularly existant for small ventures and could explain the current rise of virtual biotech firms. Despite the attention in academic research, there have been only a few studies which look into the current critical drivers of value to gain competitive advantage in this highly dynamic segmented market. The aim of the study is therefore to increase the understanding of critical factors for market access, particularly for small ventures and to develop a tool that provides support for market access decisions. This tool will allow for practical use and will guide managers in small ventures in the period prior to a new product launch in the market.

The results of the empirical research were mainly achieved through an online survey and in-depth interviews within companies. The selected sample consisted of fourteen companies with a mean size of 1.64 and a mean age of 6.71 year. Other respondents' characteristics are related to the company's turnover, funding and presence of a cash cow, phase of the main product, product type, product indication, management team's business experience and management team's international experience.

The results concerning the market access showed a trend that a small majority (64.3 percent) of the companies believe their international market access to be problematic or very problematic To apply a causal approach, barriers were identified and their influence on perceived difficulty of international market access was explored using Rough Set Data Analysis (RSDA). This type of analysis was applied to determine underlying trends in a small sample, using data on a low level of measurement and with a somewhat fuzzy character. Results of RSDA were presented in so-called 'decision rules'.

From the analyses, it appeared that product type, target product profile requirements, appropriate pricing, reimbursement requirements, creating awareness, availability of financial capital, risk sharing agreements, management team abilities and regulations have some power to explain the perceived degree of difficulty of international market access. The barriers that were strongest (derived from the highest frequencies in the rules) are management team abilities and reimbursement requirements. Regarding absorptive capacity, it appeared that age and management team abilities tended to have an influence on the perceived degree of difficulty of international market access.

The results suggest that managers who know more about international market access factors realize market access to be more problematic, what supports the advantage of more guidance on international market access to small ventures seeing earlier hurdles and challenges. Furthermore, from the results it can be seen that predominantly companies with professional, experienced management teams believe international market access to be difficult.

The results offered the basis for the design of a practical, knowledge-driven decision-support tool, a so-called do-confirm checklist. The factors that were considered to be important for international market access were included in this checklist. The factors with the highest frequency of appearance in the rules were highlighted in the tool. This checklist can be applied by managers of small pharmaceutical companies concerned with clinical products and offers the possibility for improved decision making through management guidance.

This decision-support tool thus enables small-sized pharma ventures to gain better insight into the decision-making process surrounding market access and into in-house capabilities that are needed. With these characteristics, the decision-support tool could add to the Top Sector policy.

ABBREVIATIONS

ACAP = Absorptive Capacity

CRO = Contract Research Organization

CEO = Chief Executive Officer

CIP = Competitiveness & Innovation Program

CMO = Chief Medical Officer

CSO = Chief Medical Officer

CMO' = Contract Manufacturing Organization

DST = Decision-Support Tool

EC = European Commision

EIT = European institute for Innovation and Technology

EMA = European Medicines Agency E.U.

EU = European Union

FDA = Food and Drug Administration U.S.

FFF = Family, friends and fools

FP7 = Seventh Framework Program

HTA = Health Technology Assessment

H2020 = Horizon 2020

IP = Intellectual Property

IPO = Initial Public Offering

KOL = Key Opinion Leader

LSH = Life Sciences and Health

NBE = New Biological Entity

NIH = National Institutes of Health

NCE = New Chemical Entity

NHS = National Health Service

R&D = Research and Development

RSDA = Rough Set Data Analysis

ROSE = Rough Set Data Explorer

SME = Small and Medium sized Enterprise

TPP = Target Product Profile

SSP = Specialized Service Provider

VC = Venture Capital

QoL = Quality of Life

1. INTRODUCTION

1.1 Problem area

Introduction problem area

In the pharmaceutical industry market access has been gaining considerable attention in recent years. To pursue optimal market access and to achieve competitive advantage pharmaceutical companies face large challenges (Ernst & Young, 2014). Some of these challenges include meeting the requirements for reimbursement, taking into account a changed market access stakeholders' map, considering the augmented reliance on formal health technology assessment (HTA) and strategic pharmaceutical pricing.

At the moment specific 'Top sectors' such as the Life Sciences and Health (LSH) sector in the Netherlands obtain government priority. The Dutch government desires to excel in the Life Sciences and Health sector in 2025 and states that the Dutch domestic market can play a role as a gateway to fast and effective implementations of innovations which can then find their way to the international health market. Despite this attention, there is still a lack of clarity on international market access factors. Pharmaceutical companies hire consultancies to gain support in the market access process to alleviate uncertainty. The Dutch Life Science and Health Top Sector looks into several topics, like rapid implementation of new products, optimal national regulation and guidelines, education of qualified personnel, raising entrepreneurs, facilitating access to proper financing and strengthening the knowledge database to optimize the conditions for the Life Sciences industry (Topsectoren.nl, 2014), ((; Government of the Netherlands, 2014; Government of the Netherlands, 2014; Government of the Netherlands, 2014).

Besides the special attention in the Netherlands for the life sciences industry, an important European wide funding program, Horizon 2020 (H2020), started in 2014 which is the successor of the Seventh Framework Program, (FP7), Competitiveness & Innovation Program (CIP) and the European institute for Innovation and Technology (EIT). These independent funding programs had their own focus, however today these are merged in H2020 with one common focus and a better overview of all applications. H2020 is the biggest EU Research program with nearly eighty billion euro of funding available of 7 years (2014-2020) and aims at securing Europe's global competitiveness by stimulus for science and innovation (Rijksdienst voor Ondernemend Nederland, 2014). In this program a new instrument has been added with special focus on small medium-sized enterprises (SMEs). The program will offer funding for companies to find out if their innovative idea can be translated into market success, financial support for development of innovative ideas at an early and high-risk stage, concrete and easy business support and coaching from design to market, and guidance on how to identify and attract private investors (see Section 2.1.2 European Union's Horizon 2020)

From the aforementioned it becomes clear that the Dutch LSH sector and the European Union intent to enlarge respectively the Dutch and Europe's LSH global competitiveness and strengthen their support for small ventures but will these encouragements be enough for the small ventures to face the challenges in the pharmaceutical industry?

Challenges in the pharmaceutical industry

In the pharmaceutical industry some industry specific challenges have gained attention. The challenges to pursue optimal market access are partly due to different markets and the diverse requirements that countries and health authorities have for health technology appraisals and reimbursement. Despite the utmost importance of appraisals and reimbursement, pharmaceutical companies today encounter a large challenge to identify the reimbursement requirements (Nooten, 2012).

Within the industry the market access stakeholders' map is changing, consequently influencing as well the market entry potential of companies. The traditional stakeholders involved in the market access process remained but currently new non-clinical stakeholders are included in the process such as payers and patients (Capgemini Consulting, 2009).

Another trend involves the augmented reliance on formal health technology assessments to control the adoption and diffusion of health technologies. However, HTAs create in combination with budget constrains, hurdles for manufacturers to ensure successful product commercialization (Nooten, 2012), (Drummond & Towse, 2014).

Accelerated product time-to-market and strategic pharmaceutical pricing, the determinants of evolution and distribution of cash flows across time and countries, also play a crucial role regarding market entry and have large implications for future profits.

Currently these pressing subjects and associated barriers obtain more attention and global strategies may be concerned with establishment of consistency in pricing and reimbursement levels and more transparent market entry requirements across different markets (Verniers, 2011).

Another risk for pharmaceutical companies is the threat of generics. These medicines, with the similar or same structure as the (expired) patented drug, are associated with relatively lower investment and less risk. In the past large pharmaceutical companies' high returns arose from inter alia enforceable patents rights. Many of these companies, able to develop traditional blockbuster medicines, now face a '*patent cliff*', as key patents in these major pharmaceutical companies' portfolio face imminent expirations with no or little replacement by newer products capable to generate blockbuster-size revenues. This also contributes to the changes in the landscape of pharmaceutical industry with recently fusions of millions of dollars.

The challenges need to be taken into account to achieve successful product commercialization which becomes more crucial as Research and Development (R&D) expenditure continued to rise over the last decade. Although a significant decline in R&D productivity has been measured, the number of new drugs approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) has been relatively unchanged each year; indicating a declining profitability of a marketable output per unit of R&D input (Gleadle, 2012), (Cockburn, 2004).

Escalating health care costs due to growing prevalence of chronic diseases and increased ageing of the population, heightened investors' expectations and increasing sophistication of insurers and regulators compel globally pharmaceutical companies to become more effective at pursuing the available resources of revenue (Rankin, 2003).

Innovation process and financial models

To improve understanding financial capital problems within the pharmaceutical sector, insight in the innovation process of pharmaceutical products will be introduced below.

In the pharmaceutical industry the complete cycle from a potential drug idea generation up to market introduction can be divided in four stages (Raaphorst, 2012); these contain 'discovery and development', 'preclinical phase', 'clinical phase' and 'approval and marketing'.

In the *discovery and development phase* the innovative ideas can come from individuals, universities, government-funded research and firms. In the discovey phase companies often screen for potential drug candidates by means of testing large amounts of compounds until interesting drug agents are found to continue the preclinical phase.

In the *preclinical phase* the potential drug agents will be further tested in complicated testing models, to verify reasonable safety for initial use in humans and for efficacy, to find out whether the compound justifies commercial development.

The *clinical phase* consists of three different clinical phases namely: phase I, II and III. In the first clinical phase efficacy and safety is proven. In phase II the drug can be tested on small groups of

patients with the targeted disease. In the final phase, phase III, the drug can be tested on an extended group of patients to measure the efficacy and see long-term results.

The final phase is the *approval and marketing phase*. Results of the preclinical studies will be sent for approval to regulatory organizations. These organizations, like the FDA or the EMA analyze the results on significant benefits of the new medicine in comparison with competitor products. After approval, clinical phase IV can be started to gather further effectiveness data. In this phase health care cost agencies assess whether the agency should fund or cover a drug for treating the target patients group.

The development of products in the pharmaceutical sector can be differentiated from other sectors by long development cycles of products. The development of new products is associated with high risks and requires large investments to finance the R&D costs (e.g. clinical trials). Small ventures are assumed to be the motor of life science sector and are important for the delivery of novel therapies and solutions for patients, however these small to medium enterprises do not have sufficient resources to finance all the development costs of their novel discoveries. Small ventures developing a new drug are highly dependent on alternative funding because they lack sales-driven income.

Several financing resources are presented in literature such as business angel(s) (funds), regular bank financing, subsidies and family, friends and fools (FFF), venture capital (VC) or initial public offering (IPO) (HollandBIO, 2014). Startup companies have access to many grants which enables them to perform discovery research. By the time companies find interesting drug opportunities for preclinical testing the companies' resources often run dry and the companies have to attract new investments. This moment indicates a financing gap and is also referred to as the '*Valley of death*', which is a crucial moment for a company and could partly be taken care of by investments of large pharmaceutical companies.

So it appears that small ventures face large challenges prior to international market access which is complex due to technology development process, changes in regulations and the dynamics in the industry.

1.2 Research objective

Following from the problem area, small pharmaceutical ventures, with financial restrictions, must manage their market entry and must take into consideration strategic considerations. Small companies need to assess and understand the role of international market access factors.

One of the case study companies wishes to explore the landscape of market access and the critical success factors that will support its market access. It desires to develop a strategy for effective global launch of their medicine to meet revenue and profit expectations and to gain favorable market access regarding the competitive environment in the pharmaceutical industry. However, due to the lack of clarity and transparency of the market access factors and the lack of experience of the company in this process, the call for external expertise to support commercialization of the product is highly attractive. Some pharmaceutical companies hire consultancies to gain support in the market access process to alleviate uncertainty. This process brings along high consultancy costs but could influence the product's time-to-market and future profits.

This research will explore and discuss the critical factors for small ventures in the pharmaceutical industry in the Netherlands to support decision making prior to market entry in the industry. After exploratory research, by means of a survey based on current knowledge from literature, it is expected that a decision-making support tool can be generated for small ventures for pharmaceutical companies.

1.3 Research questions

The main research question for this study is: *What are the critical factors for market access by small ventures in the pharmaceutical sector and how can these factors be elaborated in a market access tool?*

In order to answer the main research questions the following sub questions are answered:

1. What are current trends in the pharmaceutical industry that influence the need for a decision-support tool for international market access?
2. Regarding the decision-support tool (DST):
    a. How can a decision-support tool contribute to decision-making processes?
    b. What are the basic categories of decision-support tools in scientific literature? And which DST should be applicable to develop a decision-support tool for small pharmaceutical ventures?
    c. Which requirements should a decision-support tool for international market access by small ventures satisfy?
3. What are the potential factors that influence international market access as mentioned in scientific literature? What are the critical factors in market access in practice of small ventures, concerning:
    a. The product, like product profile, comparators, pricing and reimbursement.
    b. The firm, including size and its networks, like lobbying and negotiating and access to distribution networks.
    c. The sector and market, involving market size, national regulations, financial incentives, payers and patients influence and health technology assessment.
4. What can be concluded about the critical factors for international market access in the pharmaceutical industry?
5. How should the critical factors be elaborated in the decision-support tool for small pharmaceutical ventures? How will the decision-support tool look like in terms of content and design? How should it be applied?
6. What could be the implications of these findings for:
    a. the small ventures in terms of new market access strategies?
    b. the Life Sciences and Health sector?

1.4 Research approach and flowdiagram

In this section you will discover the approach that has been used in this study.

Literature review

A literature will be performed and will include:

- An explorative desk research to gather more knowledge current trends within the pharmaceutical industry.
- A study on decision making and decision-support tools to understand and gain more knowledge on how to design a support tool.
- A study on characteristics of small ventures to explore chacteristics that need to be taken into account for the design of the tool.
- A study to find relevant background information and critical factors affecting market access in the pharmaceutical industry especially for small ventures.

Data collection and model estimation

To form a proper database an explorative desk study will be performed to collect life sciences and health companies in the Netherlands. Subsequently sample will be selected and include small ventures with drugs that need to encounter clinical trials. Data needs to be collected to gather information on

the critical factors for market access factors in the sample of small pharmaceutical ventures. The data will be collected by means of:

- An online survey
- In-depth interviews

The data will be analyzed and critical factors will be selected after which Rough Set Data Analysis (RSDA) can be performed to recognize embedded trends in the small slected sample and to find causality between several selected potential barriers and international market access.

Development of the decision-support tool and validation

Then the obtained data will be used to integrate the factors into a decision-support tool for market access that builds upon experiences of managers and literature. The validity of the proposed decision-support tool will be tested by means of validation interviews with an expert in the industry.

1.5 Flowdiagram of the outline of the report

To summarize, the report will follow the research approach with a literature study on trends and developments in pharmaceutical and biotechnological industry, the characteristics of small pharmaceutical ventures, knowledge on decision making and decision-support tools and potential barriers for small pharmaceutical ventures. After the literature study, the methodology for the quantitative and qualitative research will be explained. In addition to the results, the design of the tool, the validation and the discussion will be described and suggestions for further research will be mentioned.

An overview of the outline of the report can be found in Figure 2.

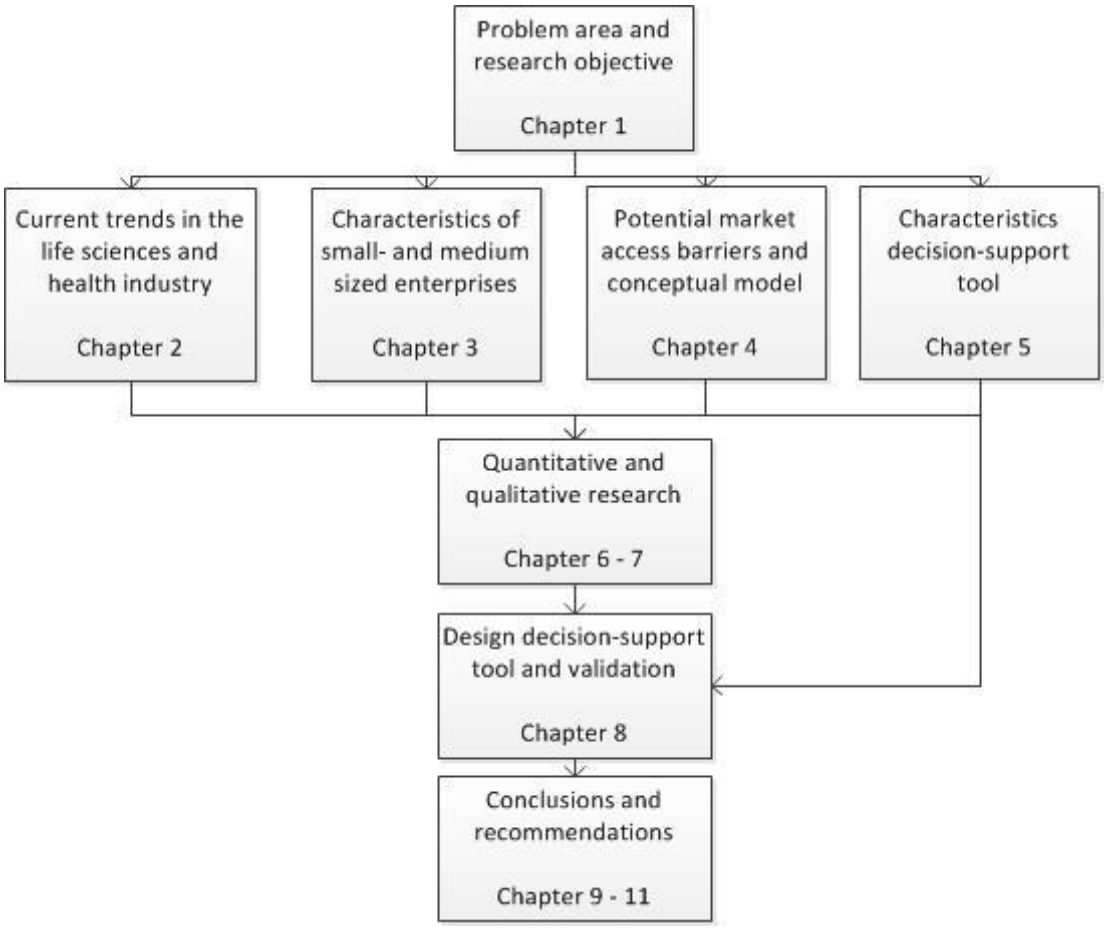


Figure 1: Overview of the outline of the report

2. DEVELOPMENTS AND TRENDS IN THE PHARMACEUTICAL AND THE BIOTECHNOLOGY INDUSTRY

This section will illustrate the eigth Dutch life sciences and health clusters in the Netherlands which are attractive locations for small ventures to settle. After this changes in amount of employees working in pharmaceutical and biotechnology companies can be seen, showing that the amount of employees in micro and small companies rose contradictonary to large firms where the amount of employees relatively declined in the recent years. This is an interesting indication as the focus of this study is on small ventures.

Afterwards current trends in the pharmaceutical industry will be considered which will reveal some potential market access barriers for small pharmaceutical ventures and will be helpful to understand why a decision-support tool could be useful for managers prior to international market access.

2.1. Developments in the Dutch the pharmaceutical and biotechnology industry

Dutch life sciences and biotechnology clusters

Several research parks or science parks exist in the Netherlands ; in total there are eight life sciences and biotechnology clusters which can be seen in Figure 3.

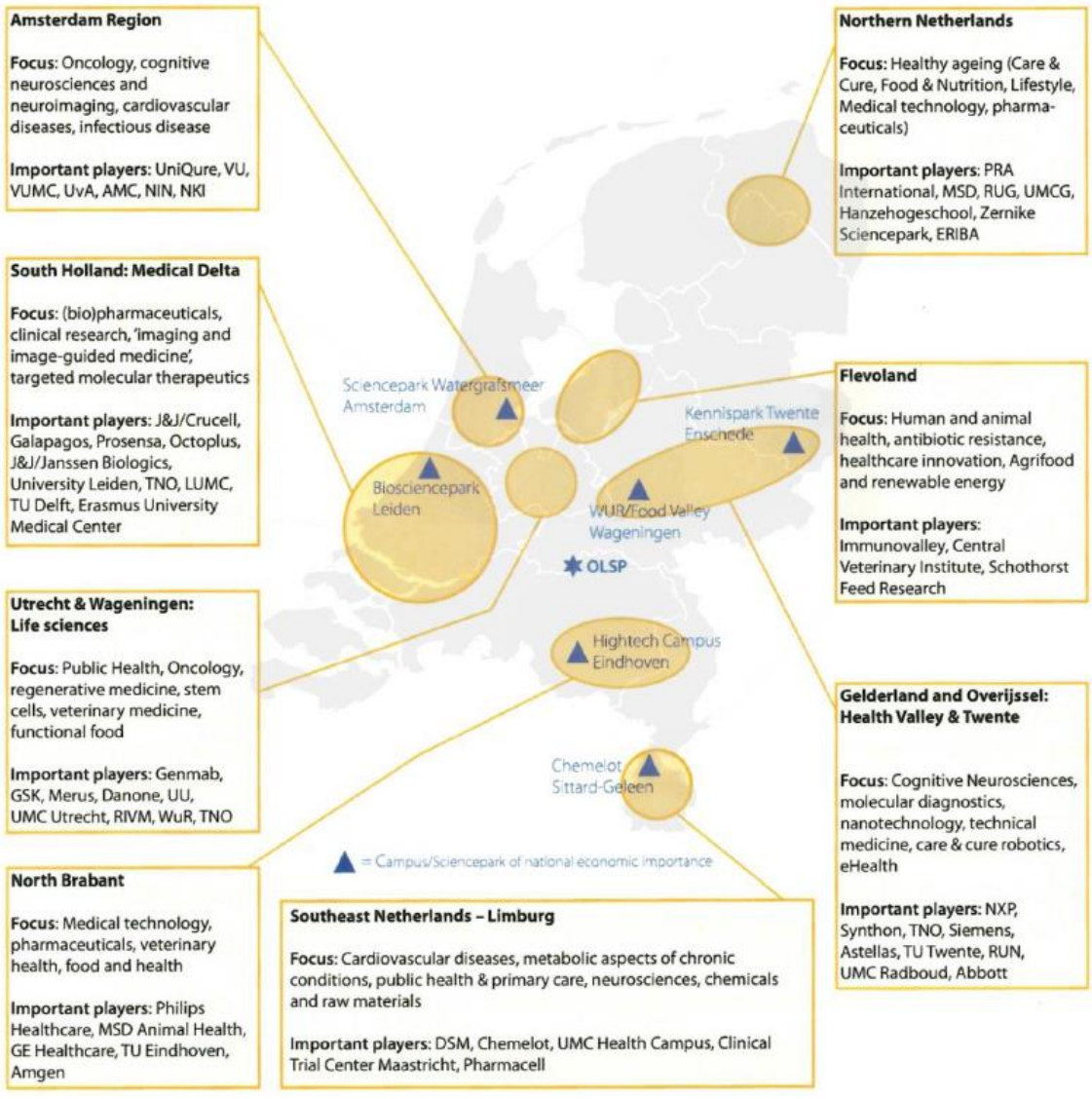


Figure 3: Overview of life sciences and biotechnology clusters in the Netherlands (Raaphorst, 2012)

These cluster include Science Park Amsterdam (Amsterdam area), Utrecht Science Park (Utrecht and Wageningen area), Bio Science Park Leiden (South Holland: Medical Delta area), Technopolis Delft (South Holland: Medical Delta area), HighTech Campus Eindhoven (North Brabant area), Science Park Maastricht including Chemelot (Southeast Netherlands- Limburg area), Pivot Park Oss, Health Valley & Twente and there is a science park in Northern Netherlands namely Zernike Science Park Groningen. All of these research clusters include companies active within the pharmaceutical or biotechnology sector and only five of these clusters contain a university campus site. The Leiden Bio Science Park, fully dedicated to biomedical life sciences, is the leading life sciences cluster in the Netherlands and belongs to the most successful science parks in Europe.

Current Dutch Life Sciences and Health enterprises and employees

In recent years the amount of Dutch Life Sciences and Health companies and the number of employees in the industry have slightly changed (The Decision Group, 2014). As mentioned before company Organon was purchased by Schering-Plough in 2007. Later on in 2009 Schering-Plough merged with Merck & Co. and in 2011 MSD decided to close down its discovery research department in Oss. This led to heavy debates in the Netherlands but these could not prevent the cut of jobs of 500 employees. Large firms in the Netherlands decreased their number of employees, as could be seen in Figure 4C and 4D.

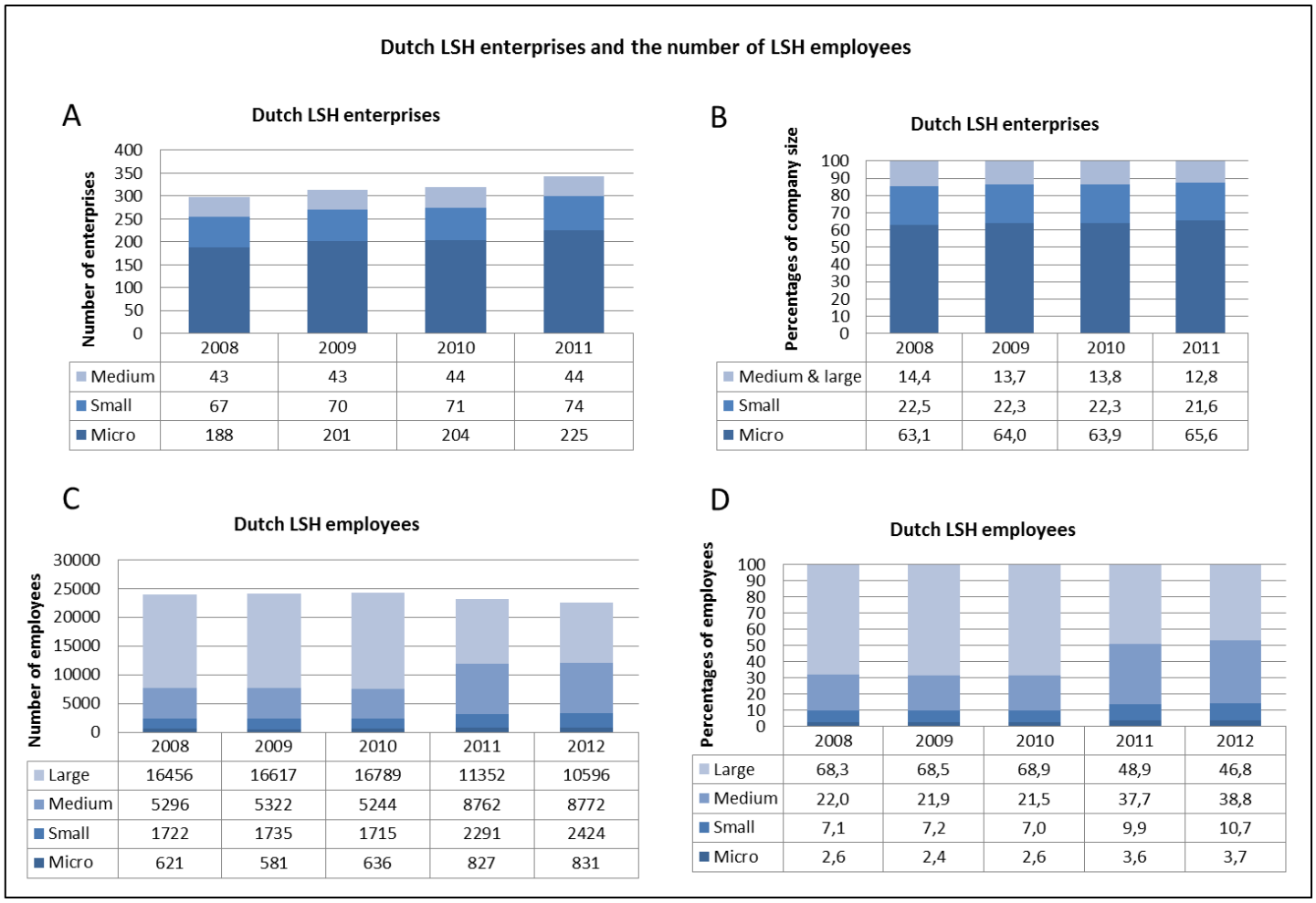


Figure 4: A and B) Overview of the number and percentages of Dutch Life Science and Health companies and C and D) the number of Life Science Health employees grouped per size of the companies. Micro includes companies with 1-10 employees, small 11-50 employees, medium 51-500 employees and large >500 employees (The Decision Group, 2011) (The Decision Group, 2012) (The Decision Group, 2013) (The Decision Group, 2014)

The decrease of employees of large firms can partly be explained by the loss of 500 employees in the case of MSD and also the loss of 500 employees for the company Abbott Laboratories in Weesp in 2010 (Reuters, 2010). As a positive effect, many of the fired employees started small ventures and this explains the rise of SME personnel and the amount of small ventures.

Another reason for the augmentation of the amount of small ventures could be attributed to the rise in virtual life sciences and health companies. These companies aim to have a low number of employees and outsource most of the activities such as discovery, preclinical trials and clinical trials. Virtual companies strive to keep the company as small as possible because they have large risks because many products development fails. Investers support this model in which the fixed cost could be maintained at a low level.

A relative augmention of small ventures and an increase of personel in small ventures strengthens the need for more guidance to the managers to let them gain better insight in the decision-making process prior to market access.

More figures on the Dutch Life Sciences and Health sector can be found in *Appendix A: Dutch Life Sciences and Health industry numbers*.

Stimulus for the Dutch life sciences and health industry

In 2000 the program BioPartner of the Ministry of Economic Affairs started to bring a stimulus to the Dutch life sciences industry by contributing to a stronger positive entrepreneurial culture and providing support for startup companies. Besides this stimulus, Dutch innovative projects are stimulated by Top Institute Pharma (TI Pharma) and the Centre for Translational Molecular Medicine (CTMM). TI Pharma's mission is: "*To establish, support and manage public-private collaborations between academia and the (inter-) national pharmaceutical industry in order to create 'health and wealth"*. This institute stimulates and supports programs by means of funding, secretarial services, finance, intellectual property, communications and education & training and IT (TI Pharma, 2014). The CTMM, a public-private partnership for translational research, performs research related to medical technologies in the area of personalized treatments and aims to become a leading Dutch-based innovator of Molecular Diagnostics and Molecular Imaging technologies.

To further promote the Life Sciences industry the Dutch government appointed Life Sciences and Health as one of the nine Top Sector Policy pillars which will be discussed later in more detail.

More information on the history and the developments of the last 25 years in the pharmaceutical and biotchnogy industry can be read in *Appendix B: History and development in the pharmaceutical and biotchnogy industry*.

2.2 Current trends in the pharmaceutical industry

This section describes recent trends which are specifically relevant for this industry. In the dynamic pharmaceutical market, companies are scrambling to adapt their commercial models to current challenges. The dynamics bring the opportunity to the industry to incorporate new understanding on what drives the value of the product, to take an agile approach to the market and to become an enabling organization which goes along with the exploration of a variety of new business models (Ernst & Young, 2014)

Several trends in this industry will be described including national and European supportive programs, diverse reimbursement requirements and the rising importance of health technology assessment. As well you will get acquainted with the values of changing stakeholders involving the rising influence of patients.

National top sector policy

The Dutch government desires to excel in the Life Sciences and Health sector by 2025 and wants the Dutch domestic market to play a role for innovations that could also be brought to the international market. The position of the sector is auspicious and at the same time, challenging. The LSH report states: '*the rising demand for health care generates chances, the rising cost of health care a task'* (Life Sciences & Health, 2011). The life sciences and health sectors have to realize high quality and affordable health care to sustain a high quality of life and control of the health care cost. The sector invests two billion euros in the development of health care solutions yearly and these investments could also allow for cost savings in the health care industry.

The LSH sector works with a management organization that represents the stakeholders in the Life Sciences and Heath industry. With the help of taskforces the management organization works on subjects like innovation contracts, financial support, human capital, international trade and regulatory activities. The management organization supports the entire chain for knowledge and innovation which is linked to their working model: "discovery, design, deploy" (Life Sciences & Health, 2011). Together with the different stakeholders the sector: articulates the demand, generates a laboratory for experimenting with developments in specific fields such as E-health, and monitors innovations to stimulate rapid replacement of old treatments.

Despite the attention of the LSH sector and the efforts of the taskforces on several topics - like rapid implementation of new products, optimal national regulation and guidelines, raising entrepreneurs, facilitate access to proper financing - there is little guidance and transparency on the required set of factors that have to be addressed to achieve international market access.

European Union's Horizon 2020

Besides, the attention in the Netherlands, Horizon 2020 (H2020) was started. This is the successor of the seventh Framework Program, (FP7), Competitiveness & Innovation Program (CIP) and the European institute for Innovation and Technology (EIT). H2020 is the biggest EU Research Program with nearly eighty billion euros of funding available spread over 7 years (2014-2020) that aims at securing Europe's global competitiveness by stimulating science and innovation (Rijksdienst voor Ondernemend Nederland, 2014). In this program a new instrument has been added with special focus on Small Medium-sized Enterprises (SMEs). Figure 5 shows additional information on the SME instrument and activities supported by the instrument.

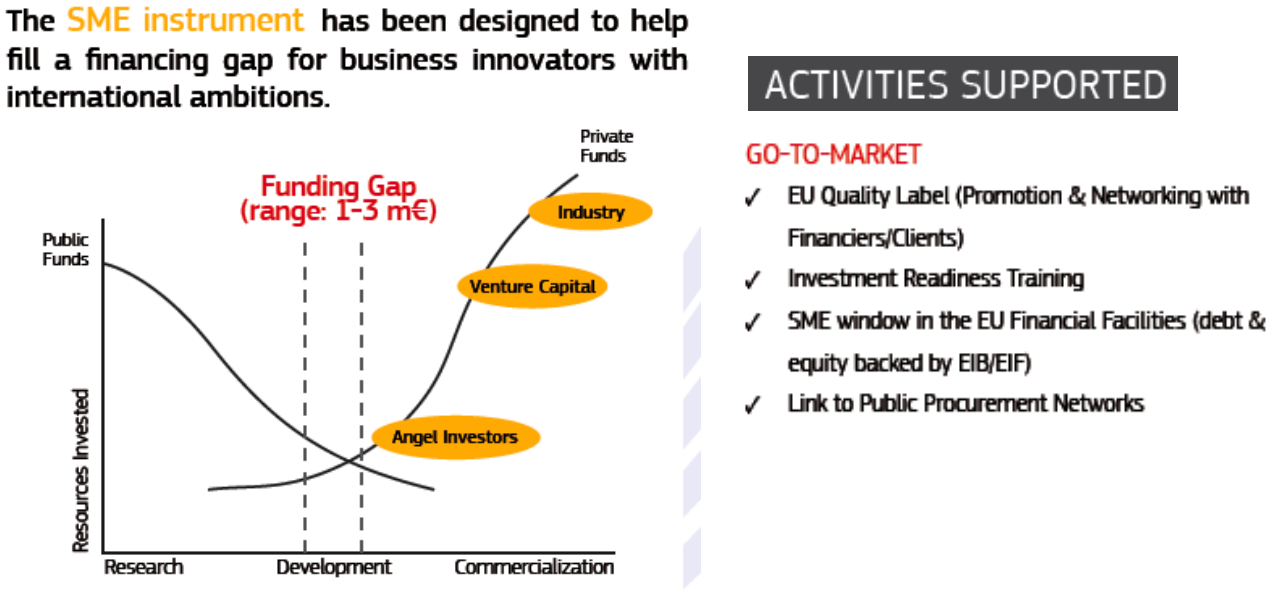


Figure 5: Horizon 2020 SME instrument by the European Commission. Obtained 29th of April from The SME instrument: Your highway to innovation (Rijksdienst voor Ondernemend Nederland, 2014)

It will offer funding and financial support for development of innovative ideas at an early and high-risk stage, business support, coaching from design to market.

The instrument ascribes projects to three different phases namely *Concept and feasibility*, *R&D, demonstration and market replication* and *commercialization* which facilitate the European Commission (EC) to determine the development stage of a project and associated funding. In the last phase, which is the most related to this research, single SMEs will be provided with indirect support measures as well as access to financial facilities rather than direct funding. This phase '*aims to promote the implementation and successful commercialization of innovative solutions by facilitating access to private capital an first customers as well as offering support services'* (Rijksdienst voor Ondernemend Nederland, 2014). Participants successfully rounding off phase 2 will be offered to benefit from a range of additional services such as facilitated access to risk finance, investment readiness support and a full range of Enterprise Europe Network services to help successful commercialization of the project during Phase 3. The main focus of aid will be financial facilities and risk finance (public/private) support for SMEs.

It becomes clear that H2020 program supports small ventures and facilitates services to alleviate financial concerns. The EU intends as well to enlarge Europe's global LSH competitiveness and strengthens its support for small ventures but more guidance for these SMEs may be desired.

Rising R&D expenditure & health care cost

One of the challenges in the industry include the rising R&D expenditure and health care cost. Achieving successful product commercialization has become more crucial as R&D expenditure continued to rise over the last decade. Although a significant decline in R&D productivity has been measured, the number of new drugs approved by the FDA or EMA has been relatively unchanged each year; indicating a declining profitability of a marketable output per unit of R&D input (Gleadle, 2012), (Cockburn, 2004).

Health care costs are as well rising. The worldwide life expectancy for humans increased over the years as The Human Mortality Database shows the growth from 45 (1950) to 68 years (2013). This is one factor that contributes to these costs. The augmenting ageing of the population, declining gap between developed and developing countries which will increase governmental and private spending on health care, growing prevalence of chronic diseases, heightened investors' expectations and increasing sophistication of insurers and regulators, compel small ventures and other pharmaceutical companies globally to become more effective at pursuing the available resources of revenue (Rankin, 2003), (The Decision Group, 2014).

Different markets, countries and health authorities with diverse requirements for health technology appraisals and reimbursement

Another challenging trend is related to the evidentiary requirements for successful reimbursement which are substantial but vary across markets. Despite their utmost importance, pharmaceutical companies today encounter a large challenge to identify the varied reimbursement requirements. Some of these requirements include evidence for an unmet need, a value proposition showing clinical, evidence for patient value and economic value and drawing comparisons with (in)direct comparators (Nooten, 2012), (Kantar Health, 2014).

An illustration of difficulties in different markets of the medicine Xofigo from the pharmaceutical company Bayer can be found *in Appendix D: Appraisal process of the drug Xofigo*.

Especially for small ventures, which often do not have experiences with previous commercialization processes of products, the differences between the process in countries is a large challenge for potential international product commercialization.

Augmented reliance on formal health technology assessment (HTA)

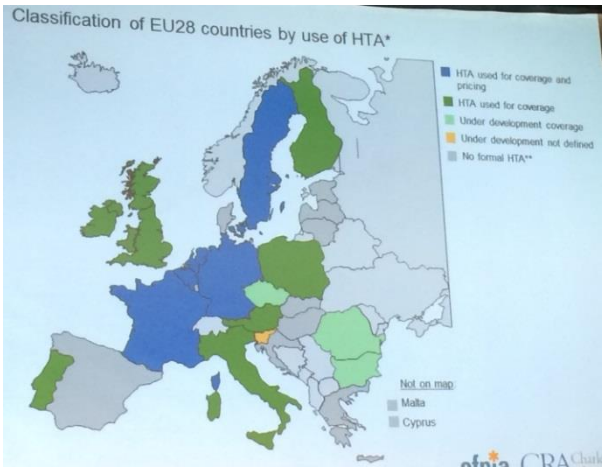


Figure 6: Reliance on HTA in Europe. Presentation 'Reimbursement in Europe' in Turin in May by EFPIA (EFPIA, 2014). Countries indicated in blue: HTA used for coverage and pricing. Green: HTA used for coverage. Light green, under development coverage, yellow: under development not defined Grey: No formal HTA

Similarly, the health technology assessment (HTA) use differs per market. The usage of formal HTAs is growing to control the adoption and diffusion of health technologies. Also an increased reliance on HTAs, to inform pharmaceutical pricing and reimbursement decision-makers, can be seen (Marchant, 2010). In several countries in the EU HTA is used for coverage and pricing, but in others only for coverage or is it not used at all (EFPIA, 2014).

However HTA creates, in combination with current budget constraints, hurdles for both the small and the large pharmaceutical companies to ensure successful product commercialization (Nooten, 2012), (Drummond & Towse, 2014).

Strategic pricing

Closely related to the subject of reimbursement is strategic pricing. The pharmaceutical industry differs from many other industries by the existence of regulated demand and supply. Some characteristics in this industry include: the prescription of medicines are subject to derived demand, the prescription of medicines are considered to be 'negative goods' and medicines are experience goods, which means actual utility cannot be determined until products have been used (Kolassa, 2009). These characteristics are taken into account in strategic pricing for pharmaceuticals.

Recent discussions augmented on the pricing structure, a controversial aspect of for example rare diseases and orphan drug development, as some orphan drug pricing lately reached unprecedented levels. National Institutes of Health (2010) reported that orphan drug affordability enlarges contentious relationships among players in the environment. Discussions are conducted over the justifiability and sustainability of prices and socially acceptable pricing limit. Small ventures inexperienced with setting prices may have difficulties regarding strategic pricing.

An example of discussions on an outrageous price product can be found in *Appendix E: Outrageous pricing of the drug Solvaldi*.

Changing market stakeholders' map

Within the industry the market access stakeholders' map is changing, accordingly influencing the market entry potential of companies. The traditional stakeholders involved with market access process were prescribers, Key Opinion Leaders (KOL) and regulatory agencies. The primary care physicians in the past made the decisions about what medication to buy or what drugs or treatments to prescribe. Now new non-clinical stakeholders are included in the process such as payers and patients who influence the uptake of the drug by the markets (Capgemini Consulting, 2009). Payers and patients are increasingly taking the lead in decision-making and influence the physicians' decision-making in terms of medicines that offers the best value for their money, economic benefits and a positive improvement in health outcomes.

New stakeholders are gaining influence due to the development of sophisticated health information technology. Mobile health technology is developing and possesses a number of unique attributes to become a powerful behavior change agent in the transformation of health care (Gottsch, 2014). Mobile technology currently provides real-time access to digital health information, supporting diagnosis and monitoring. Moreover, it gives the opportunity to stimulate patient adherence and compliance (Ernst & Young, 2014). Pharmaceutical companies, though, need to be aware that health care apps increase awareness, engage and educate and ultimately modify behavior of patients and alters their influence.

Social media platforms enable the sharing of health information. The combination of social media and health information technologies creates benefits for the patients. The patients get access to information that in the past was not made available to them but only to the health care providers.

The expansion of health data also strengthens the influence of payers in decision-making. The payers use the data-mining tool to assess outcome-based pricing and reimbursement schemes and particular treatments' ultimate effectiveness in practice.

Small ventures that often have no experiences in discussions with the wide range of stakeholders may face a challenge before global launch.

From blockbusters to rare diseases drugs

The more patient-oriented focus of companies could be related to the shift of the industry from blockbusters to rare disease drugs. Although R&D in the medical field has added value to the world average welfare, a considerable number of diseases remains untreatable because of the lack of therapeutic modalities. The limited research and treatments can be comprehended when viewing the supply and demand. David Rohde, investigative reporter for Reuters and contributing editor for The Atlantic, mentions: "*Given the limited resources available for pharmaceutical R&D, priorities must be ranked. The sheer number afflicted and the seriousness of the disease at the issue guide the allocation of resources: the most serious diseases, and those affecting the largest populations, receive the highest priorities. […] Thus, a rationally motivated pharmaceutical company focuses its resources on those endeavors that will yield the greatest returns*." This shows that the pharmaceutical industry focused on drugs, for diseases related to large populations which were associated with mass marketing potential such as *'me-too-drugs'*. These me-too-drugs are drugs with a similar or same structure as the (expired) patented drug and have a relative lower investment and risk. With these me-too-drugs manufacturers were able the recoup their investments in the R&D cost of the drug and the FDA approval cost with these mass marketing products (Schilling, 2009), (Rohde, 2000). Many of these companies that were able to develop traditional blockbuster medicines, now confront a '*patent cliff*', as key patents of large companies face imminent expirations with little or no replacement by new drugs capable to generate blockbuster-size revenues.

BIG PHARMA MOVES FROM 'BLOCKBUSTERS' TO 'NICHE BUSTERS'

NATURE MEDICINE 2010

Yet, in order to become a market leader, a company had to diversify risk and had to explore the biotechnology area to increase its chances of coming across a radically new drug. Old pharmaceutical companies focused on small molecule medicines like the New Chemical Entities (NCEs) but started to switch to New Biological Entities (NBEs), more complex drugs, to target many severe diseases that had failed to yield to small molecule medicines (Becker & Lillemark, 2006).

To induce research development and marketing of drugs for rare diseases, the FDA established the Orphan Drug Act in 1983. The act provides: funding of grants and contracts for clinical trials and tax breaks on research costs as 'push' incentives. Moreover, the act supplies 'pull' incentives such as guaranteed market exclusivity (up to 7 years in the US and up to 10 years in the EU) for

companies putting drugs for rare diseases on the market. This exclusivity offers significantly more protection from rivalry and allows companies to recoup their development costs and earn a rate of return (Drummond & Towse, 2014) (Rohde, 2000).

These incentives are applicable to orphan drugs, drugs for rare diseases that are life threatening or serious debilitating. However, the definition of 'rare diseases' differs per area. A 'rare disease' in the US is viewed as being a disease or condition affecting fewer than 200 000 patients (6.4 per 10 000 habitants) and in the European Union as a disease with a prevalence of five percent per 10 000 or lower (Drummond & Towse, 2014).

The orphan drug market is today one of the fastest growing niche markets of the pharmaceutical industry and involves small emerging companies and some of the most global pharmaceutical companies. According to FierceBiotech (2012) the growth rate of the revenue for orphan drugs clearly outperforms the growth rate of the revenue for the control group of non-orphans therapies, respectively 25,8% and 20,1%. (Lupo, 2014). In *Appendix F: The top selling orphan drugs 2020 and launched in 2013* can be seen and highlights the growing importance of orphan drugs in the pharmaceutical industry.

To further stimulate the development of products for rare disease designations or a special status 'labels' for a new medicines were created to deliver advantages for those developing companies regarding fast track approval, tax incentives for clinical research, enhanced IP protection and marketing rights etc. Lately a guidance for the industry was published to provide more information and more transparency in the industry on the designations procedures (FDA, 2014).

Consolidation in the pharma industry

Another trend which could be attributed to the switch to niche markets, is consolidation. Fusions of millions are emerging in the pharmaceutical industry. Companies could merge to reinforce their specialism which can result in less competition in their niche market. Another reason for a company to merge could be to strengthen (or broaden) the company's knowledge or to enlarge its market position within a specific field. When a merger leads to a large (niche) market position for a company this new position can have implications for drug prices in the market for this specific field (Brink, 2014).

Today, big pharmaceutical companies reject the company's activities with which the company cannot achieve a leading market position. Whereas the small companies buy competitors to enlarge their size and to strengthen their position in the market. Several examples in the market are GlaxoSmithKline (GSK) that withdraws from the participation in oncology medical field, while Novartis enforces its position in this area. It could also be an argument for Pfizer that aims to acquire AstraZeneca, a company that holds a wide portfolio of oncology products. A recent example comprises the agreement between Novartis and GSK. Tuesday 22nd of April 2014 Novartis and GSK reached an agreement on Novartis acquirement of GSK's oncology's activities, while Novartis in turn will sell its vaccines to GSK and its animal medication to Eli Lilly and Co (Armstrong, 2014).

Further consolidation will occur in the pharma industry over the next ten years. The type of consolidation will not consist of 'mega mergers' but will more likely be an increasing number of very targeted acquisitions to supplement a core capability. Companies will refocusing their portfolio as well to create a more clear strategic roadmap for investors (Eyeforpharma, 2014).

An increase in consolidation in this oligopolistic market can have implications for small ventures, as small ventures may become targets for acquisitions to strengthen large pharmaceutical company's capabilities.

2.3 Summary and conclusion

Many mergers and acquisitions present in the Netherlands changed the landscape of the companies in the Netherlands. Jobs losses were the result and subsequently personnel started a small venture, as this was shown by a rise of SME personnel and the amount of small ventures. The government strives to

support the life sciences industry by providing funds and grants and by specific programs such as the Top Sector policy. Similar to national support there is European support by means of the program H2020, a stimulus to secure Europe's global competitiveness in this industry and has special focus on small ventures.

These programs support pharmaceutical companies that today face many challenges in the pharmaceutical industry. The industry shows rising R&D expenditure and health care cost that put emphasis on successful product commercialization. However, companies in the international pharmaceutical market have to encounter different requirements in diverse markets for health technology approval and reimbursement. Also the augmented reliance on HTAs and the specificity of the assessments per country, have implications for successful commercialization of products. The value drivers of new market stakeholders have to be comprehended as well as payers and patients increasingly participate in decision-making.

Consolidation in the pharma industry occurs and will rise. Large pharmaceutical companies reject those activities that do not bring a leading market position and refocus their portfolio to stay competitive.

In this industry trends have been identified that reveal challenges which could be barriers for small ventures prior to the launch of their products worldwide. In this study the gravity of the barriers for small ventures will be analyzed to address barriers that should be included in the decision-support tool. This tool will be designed to help managers of small ventures with decision making related to market access fot their product.

3. TECHNICAL AND PHARMACEUTICAL SMALL VENTURES

3.1 Characteristics technical and pharmaceutical small ventures

In the previous section the current trends in the industry have been described which could form potential barriers to international market access for small ventures. In this section the characteristics of technical small ventures and pharmaceutical companies will be described in order to get insight in the difficulties of small (pharmaceutical) ventures that could play a role regarding market access. The characteristics of small ventures are related to the outsourced activities, the uncertainty of the technology and human and financial capital and will be described below.

- One of the challenges technological small ventures face is the uncertainty in development extent of their new technology. In some cases where experience or knowledge is lacking, small ventures buy knowledge or collaborate with external parties. This can however evoke the not-invented-here syndrome (see section *Consolidation of the pharma industry*). Also pharmaceutical ventures buy knowledge or collaborate with external parties when knowledge is absent. This has advantages such that ventures do not need to invest in expensive research equipment and experiences of other parties can accelerate ventures' development processes. In this industry however the disadvantage like the not-invented-here syndrome would play less a role as many activities of small to medium sized pharmaceutical companies have been outsourced over the years to external parties.

- Alliances are also of added value for small ventures and these enable the transfer of knowledge between firms. An alliance can provide access to complementary skills and resources and joint creation of knowledge could be a result (Schilling, 2009). Collaborations pose different trade-offs in terms of cost, control, for the development of new competencies and speed. Collaborations are as well highly important in the pharmaceutical industry. Small pharmaceutical companies strive to achieve a partnership or strategic alliance with a larger company especially for the financial back up, the experience and knowledge present.

- Initially a technology bares uncertainty, since the technology is still in the development phase, information on the added value, target population or the outcomes is lacking. Gradually the technology implications become less uncertain. The uncertainty of the implicational extent of the new technology in small pharmaceutical ventures, however, may be lower as most of these firms focus on (specific) disease areas and patients. Moreover the development of new pharmaceutical products is considerably costly, time-consuming and extremely risky (Schilling, 2009). Typically in the pharmaceutical industry the percentage of failed projects is high (Hynes Iii, 2009), (David, Tramontin, & Zemmel, 2010).

- Another challenge for small ventures is the missing track record which make evaluation of the value of their potential product more difficult. These uncertainties contribute to the difficulties in the determination of the value of new technologies which is highly important when rival technologies and communities compete for dominance. This also counts for small pharmaceutical companies and convincing data and narratives are needed to influence different stakeholders.

- The lack of experience of small ventures with suppliers and customers adds difficulties. In general when a technology is totally new, no appropriate suppliers or distributors may be present and this could lead to in-house production or distribution. In case of the customers; there may be a knowledge gap on the requirements customer value. Sometimes a firm has to withstand significant losses before these customer preferences are more defined. For a new

disruptive product no appropriate supplier exist and in-house production could be a result. Distribution of the product however will be easier managed as distributers are approaching the small pharmaceutical ventures to distribute the product. Small pharmaceutical ventures with a highly disruptive product face difficulties with doctors and patients too who may be unaware of the potential of the product, the use or the implications of the product.

- Human capital is another important aspect for a small venture. Human capital is evaluated on the presence of a combination of skills and past experiences within the management team. Human capital in small pharmaceutical companies is also of importance because the highly valued scientists have to develop the underlying product, process and services to deliver a successful product in the end (Zucker, 1998). Besides the scientists, business people with experiences, skills and knowledge are highly valued. They have to prepare and transfer the new product with accessible information to the market with the numerous stakeholders.

- For a company the appropriability, the degree to which a firm is able to capture the rents from its innovation, is of great importance due to the relative high R&D investments. Patent protection of an invention of components or combinations of components is necessary because a patent's protection excludes others from producing, using or selling the invention and facilitates a company's cost recovery. In pharmaceutical ventures due to the fact that R&D costs in this industry are considerably large, IP protection is extremely important. The patent protection or exclusivity can even be extended in this industry up to 7 years in the US and up to 10 years in the EU for orphan drugs. This extended time protects a company's product against generic drugs produced by competitors.

- Finally, small ventures need to finance their R&D costs. Often small ventures face long development times of their technology and have no sales income during this development. Small pharmaceuticals ventures often lack financial resources, as these do not yet have any approved products on the market and do not generate sales-income. Pharmaceutical firms have to perform clinical trials before a product can be approved and in comparison the R&D cost are substantially higher in this industry than in other industries. Therefore small pharmaceutical ventures, with a longer and considerably more expensive development process are in a great need of financing.

3.2 Summary and conclusion

Some differences between technical ventures and small pharmaceutical ventures can be identified. Small ventures lacking knowledge buy or collaborate with external partners which could result in the not-invented-here syndrome. And whereas the uncertainty on the real extent of the new technology in technical companies is high, this may be lower in pharmaceutical ventures as they focus on a specific disease. A difference is the large reliance on human capital in pharmaceutical ventures as scientists and business people are highly valuable. IP protection is important for both technical and specific pharmaceutical companies but for pharma ventures this is crucial. Finally, financial resources are of importance for both technical and pharmaceutical companies.

These characteristics of small pharmaceutical companies offered insights on the importance of some resources which could be potential barriers for small ventures prior to market access. Small ventures face the abovementioned challenging trends and need to adapt and optimize their limited resources to reach international market access. The decision-support tool that will be designed will take into consideration the important small ventures characteristics to provide guidance to managers prior to international product launch.

4. DESIGN OF DECISION-SUPPORT TOOL FOR INTERNATIONAL MARKET ACCESS BY SMALL PHARMACEUTICAL VENTURES

Today, pharmaceutical companies face several challenges in their highly dynamic market. Yet more research is needed to provide guidance to small pharmaceutical ventures regarding international market access. The report 'Pharma 2020: Marketing the future' (2009) stressed that in the past pharmaceutical companies typically started to think about pricing after phase III of the development but they should actually start at phase II and adopt a price der-risking strategy in early development (PriceWaterhouseCoopers, 2009). Some pharmaceutical companies hire consultancies specialized in pricing, reimbursement and market access to acquire the knowledge for strong market access strategies in different markets to alleviate these market access challenges. To allow small sized pharma ventures to gain better insight in the decision-making process and provide in-house capabilities a decision-support tool is developed in this research.

The following questions will be addressed: Why would is a decision-support tool be helpful? And what would be an appropriate decision-support-tool for addressing international market access for managers in small pharmaceutical ventures?

The first part of this section will describe the implications of decision-support tools in decision making. Afterwards the different categories of decision-support tools will be explained and consequently the specific choice for a checklist for this study. Then the specific requirements of the checklist for this study will be described.

4.1 Decision making and decision-support tool(s)

Decision making

Some decisions have to be made on a daily basis and others rarely. Each decision, however, can be made in various ways. The decision making approaches can be divided in different groups such as rational decisions, bounded rational decisions, flexible and creative decisions and iterative decisions in cases of bounded information. The first group belongs to the *classical approach*, with rational decisions it is assumed that all information is present and decisions will be made to maximize outcome. In the second *organizational model*, bounded rational decisions are concerned with incomplete information and the decision that will be made will be the most optimal decision. The flexible and creative decisions will be made by a group and are part of the *political and adaptive decision model*. The last model, the *process model*, anticipates in an environment where not all information is available and objectives can change. In this last model the focus is on the formulation of a set of objectives (Harisson, 1999).

Full rational decisions or choices are often not possible because of the lack of information available or other resource constraints. Many times decisions are made by following decision-making heuristics. These heuristics are cognitive short-cuts which enable people to transform complex choices in simple judgmental choices. These shortcuts are assumed to assist every day decisions as people have limited capacity to process information (Shiloh et al., 2002). These heuristics however could lead to biases in the choices. In these cases decision-support tools can help decision makers which lack information, experience or not enough knowledge regarding the decision that has to be made. For these decision makers the valuation of information is difficult and almost impossible. Decision-support tools can provide a solution for this problem by for example providing information on the value of data, by pinpointing biases or overcoming them or pre-processing data (Gottlieb et al., 2013).

Decision makers are involved with managerial decisions and often require creativity and flexibility to come to a final decision. These managerial decisions are related to long-term objectives and managers deal with incomplete information (Pelletier, 1999). Decisions can be made by a collection of individuals such as the management team and this type of decision-making is referred to

as *negotiated decisions*. Managers can also take individual decisions, heuristics ones or not, however they have to explain their rational for the decision to the company's management team and their employees.

A decision-support tool can be used to facilitate decision processes of managers in the stage prior to market access as often commercialization of a product in the pharmaceutical industry. Such a support tool however should support and illuminate the managers rather than automate the managers' decision making, according to Steven Alter's (1980).

In this study the decision-support tool is for senior managers who decide upon long term goals and are concerned with the long term planning. Long term planning is important because specific long term goals or endpoints desire actions in earlier phases of development. When managers are aware of the whole development process and the company's goals, they could incorporate requirements of endpoints in early phases of development which will alleviate hurdles for the company in a later phase of the process.

Categories of decision-support tools

Decision-support tools can be classified in different categories, namely:

- *Model-driven decision-support tools*. These tools emphasize manipulation of a statistical, an optimization, a financial or a simulation model. The tools use data and parameters provided by users in assessing a situation. Model driven tool offer recommendations on the basis of statistical data. This tool is less favorable because it contributes less to logical rules used in problem solving.

- *Communication-driven decision tools.* These tools emphasize communications, collaboration and shared decision-making support. Examples are a simple bulletin board or a threated email which intent to support such as group processes, group awareness, communication and coordination within the group (Power, 2005). This tool would support the management team decision making however it is not the most favorable decision tool in this study as the main goal of the study is not sharing information but the study aim to provide guidance on critical factors of market access to managers.

- *Data-driven tools.* These tools emphasize access to and manipulation of time series of the company's large amounts of data. The tools can be used in warehouses to allow changes in for example stock data. The aim of these tools is related to manipulation of large amounts of data which is not in line with the aim of the current study. Hence, this type is not the desired category in this study.

- *Knowledge-driven support tools*. These tools can recommend and suggest actions to managers desire specialized problem-solving expertise. The person using the tool, has to have knowledge of the particular domain and skill to solve the potential problems. A related concept to this is *data mining*. Data mining is a process of shifting through large amounts of data to produce data-content-relationships. Data mining can be used to design a knowledge-driven support tool. The data in this research will be analyzed with the Rough Set Data Analysis which could be used to produce a knowledge driven support tool. These tools have various forms like questionnaires or checklists (Power, 2005).

The *knowledge-driven tool* differs from the *conventional model-driven tool*. A model-driven tool has a sequence of instructions on how to respond to an event. A knowledge-driven tool, however, attempts to reason about a response to an event, by using logical rules and its knowledge base for problem solving. The knowledge-driven tool thus uses representations of human knowledge. In this study

knowledge of managers is obtained to design a decision-support tool and the tool is also based on human knowledge. In addition the basis of the knowledge driven tool contains heuristic methods that identify varying amounts of uncertainty in the conclusions, to obtain a recommendation. In comparison model driven tools, use statistical and mathematical methods to obtain more precise solutions (Power, 2007). Therefore a knowledge-driven tool would be more applicable in this study.
Hence, this study will generate a knowledge-driven support tool which is the most applicable tool to provide guidance on market access factors to managers.

Knowledge-driven support tool: checklist

Checklists are used by many executives as practical producers by pilots, surgeons, software engineers, industry operators and investment bankers. They use checklists to distinguish for example a bad investment or a bad move from a good one and to make sure no critical steps are missed.

Atul Gawande, the writer of exquisitely crafted mediations on the problems and challenges of modern medicine, wrote a book called *Checklist Manifesto*. In his book he addresses a problem that afflicts virtually every aspect of the modern world and the way how professionals deal with the rising complexity of their responsibilities. Gawande distinguishes between errors of *ignorance*, mistakes people make because people do not know enough and errors of *ineptitude*, mistakes made because people do not make proper use of what people know. Both have an impact on the decision-support tool in this study as managers may make mistakes because they do not know enough and because they do not make proper use of what other people know. The solution he proposes are checklists, literally-written guides in complex procedures for experts. The checklist tool is associated with advantages but disadvantages as well and these will be described.

Advantages

Checklists, a list of required factors, can clearly set out minimum steps necessary in a process and call help with memory recall. Proper checklists are explicit and offer possibility of verification. Also checklists can instill discipline of higher performance and can be a behavior changing vehicle too.

Gawande states that checklists can help to establish higher standard of baseline performance. This decision-support tool can as well force people to talk to each other about specific elements and can be viewed as a strategy to foster teamwork. Gawande describes the ‘activation phenomenon’ where people at the start get the chance to say something which activates their sense of participation and responsibility and their willingness to speak up. From this perspective a checklist as a decision-support tool encourages communication.

And as aforementioned checklists can compensates human failure from ignorance and ineptitude.

Disadvantages

The power of a checklist is limited. These lists can help experts to manage a complex problem, make priorities and stimulate people to work better but they cannot make anyone follow them and people may be reluctant and not eager to use these checklists. Moreover checklist can hinder performance when dealing with time-critical situations and checklists are not rigid which has implications for implementation. Checklist also hinders people creativity and out-of –the box thinking towards solutions unless a checklist pushed users to do so.

4.2 Requirements of the decision-support tool: the checklist

Requirements of the checklist

For this study a checklist will be developed and managers in small ventures could address this checklist to raise awareness about several critical factors which will help them in the period prior to a new product launch in the market. The checklist in this project will introduce an overview of critical factors acquired from literature, the survey among small-medium sized pharmaceutical companies and interviews with experts and in-depth interviews with companies (N=14).

Gawande describes characteristics of infective and effective checklist and these are shown in the Table 1.

Table 1: Characteristics of ineffective and effective checklists according to Gawande (Gawande, 2009)

Ineffective checklists	Effective checklists
- vague and imprecise - too long/hard to use - made by desk jockeys without function knowledge of field - try to spell out every step - turns brains off	- efficient - to the point - can be used in the most difficult situations - above all: practical

Therefore the requirements of the market access checklist for small ventures in this study should be:

- created by people who have an understanding of the situation
- brief, to the point and easy to read (Gawande 116)
- wording has to be simple (Gawande 123)
- precise and easy to use (Gawande 120)
- it should not try to spell out everything; a checklist cannot perform a 'surgical operation'. It is a list of reminders of the most critical and important elements even one's highly skilled professionals could miss (Gawande 120)
- it should be practical otherwise it will be unused (Gawande 120)
- exhaustive including all the necessary factors
- reasonably brief period of time to complete the checklist, approximately a day to assess critically all the different factors in the tool.

Specifics of the checklist for small pharmaceutical ventures

The designed checklist for managers of small ventures in the pharmaceutical industry, especially for companies in the preclinical or clinical phases of development, aids to make sure no critical steps will be missed and helps to avoid errors of ignorance and mistakes of ineptitude. The list can be of value because the small ventures lack experience and are sometimes ignorant of previous made errors. In addition, accelerated product time-to-market is one of the determinants of evolution of cash flows and therefore this tool is valuable decision-support-tool to support for the small pharmaceutical ventures that face time-critical situations.

There are two types of checklist namely the *do-confirm checklist* and the *read-do checklist*. With the do-confirm checklist people perform their jobs from memory and experience and then stop to run the checklist and confirm whether everything that was done the way it was supposed to be. In the case of read-do checklist is that people carry out their tasks and they check them off. In this study the do-confirm checklist is adopted rather than the read-do list, to give managers greater flexibility in performing their tasks. They can however take a pause to confirm of no critical factors are overlooked. The checklist that will be designed in this study will include critical factors important for international market access by small pharmaceutical ventures in the industry. The critical factors in the checklist

will not be prioritized, as the data obtains the perceived views of health care professionals, the views are subject to different preferences and consequently hard to rank.

The checklist should meet several characteristics that are associated with achieving its intended outcome to validate the present data (Smith, 2012). These are listed below:

- Does the checklist recognize the heterogeneity in the market (different countries?)
- Does the list anticipate at changes in the market?
- Does the checklist take into consideration the strengths and weaknesses of the product relative to appropriate comparators?
- Does the checklist anticipate on the management abilities?

Several disadvantages have to be taken into account. The power of checklist is limited as aforementioned because experts that manage a complex problem cannot be pressed to follow a checklist and this group of experts may be reluctant or not eager to use a checklist. This checklist will not hinder performance due to time-critical situation as the tool will be used before market entry and the time before a market entry is critical in the terms of months but not critical in terms of minutes or hours.

Finally the checklist is not rigid due to the fact that the pharmaceutical industry is constantly evolving and dynamic. This has to be emphasized and highlighted towards the users.This tool can be seen as ‘work in progress’ as new ideas and experience become available over time.

The tool focuses on managers within companies ranging from the discovery phase to phase II. And following the Pharma 2020 report (PriceWaterhouseCoopers, 2009) factors have to be considered assessed in earlier phases in the development cycle. Additionally, the checklist can be used by managers themselves or in a meeting with management team members.

4.3 Summary and conclusion

Decision-support tools can help decision makers which lack information, experience or knowledge regarding the decision that has to be made. These tools can specifically help with decisions with long-term objectives and decisions associated with incomplete information. Several types of decision-support tools are present and in this study the knowledge-drive tool will be designed because this will fit data with hidden patterns. Several advantages and disadvantages of checklist are acknowledged though a checklist is used as an appropriate tool for this study. The requirements to design an effective checklist have to be taken into account. In this study a do-confirm checklist is chosen to be the decision-support tool and critical factors will not be prioritized due to the differences in preferences of the health care experts. The checklist that will be designed for managers of small pharmaceutical ventures has to meet several characteristics that have to be checked in a later stage.

5. THEORY: CRITICAL FACTORS INFLUENCING MARKET ACCESS

The aim of this section is to introduce the factors that can be potential barriers of international market access – the factors which will be used during the quantitative and qualitative research to analyze their importance and gravity. After this analysis, it can be determined which of the critical factors form barriers and have influence on international market access. The factors will also be taken into consideration during the decision-support tool design.

Thus, this section discusses potential market access barriers factors for successful commercialization of the products obtained from the scientific publications and other literature. This collection of information led to the focus on three levels of analysis for the factors, namely: the product, the firm (micro) and the sector (meso). The macro level was excluded from the studies because pharmaceutical companies often perform and commercialize their product globally and do not specifically distinguish between countries. More details on the critical factors, per level, for international market access will be provided. Several of the described critical factors are product characteristics: pricing, reimbursement, management abilities and influence of stakeholders like payers, patients and key opinion leaders.

5.1 The product

The product factors are related to: the technical specialties of the medicines or the medical tests, the performance of the product and the formulation of the added value of the products. Several factors will be discussed in more detail such as the target product profile, comparators, pricing and reimbursement.

Product characteristics

Target product profile

The target product profile (TPP) plays an important role during the process of providing evidence for successful product commercialization. In support of specific products, as a minimum, pharmacokinetics/pharmacodynamics, efficacy, safety and immunogenicity data is needed (McGrath, 2010) (Pesanello et al., 2010).

The prior knowledge and the extent of reference product understanding drive the number and the scope of requirements needed for non-clinical and clinical data. The degree of similarity to the reference product will minimize the need for interchangeability data. The TPP data that need to be generated contains an overview of the products' characteristics such as the mode of action, the proof of concept, indications, label claim, patient convenience, efficacy and safety.

The requirements for evidence for successful product commercialization are real and substantial and evidence types such as cost-effectiveness studies, clinical effectiveness and proof of innovation differ highly among countries (Nooten, 2012). Some small ventures may find it more difficult than others to meet the clinical endpoints due to different reasons and this could form a barrier to market access.

Value Proposition

In the market access process, the value domains such as clinical, patient and economical need to be identified and defined early in the product's life cycle (Pesanello et al., 2010).

The clinical value depends on the added clinical value that the product will generate by means of efficacy and safety (McGrath, 2010).

The patient value that can be generated depends on e.g. the population at risk. Value for patients can be added by increased safety for the patients, augmented convenience for patients and improvements towards the quality of life (QoL) of patients and family.

Another value domain is the economic value domain. For this value, companies can take into account that their product can bring a safer medical organization, higher quality medical treatment and

reduction in health care spending. So companies should take into account the benefits for the payer (PriceWaterhouseCoopers, 2009) (Nooten, 2012) (Kantar Health, 2014) (Gispen-de Wied, 2013). Small ventures with a lack of experience may find it difficult to define a proper value proposition.

Exclusivity (breakthrough designation)

Exclusivity or a special status 'label' can generate numerous advantages for companies that obtain this exclusivity. Advantages are fast track approval, tax incentives for clinical research, enhanced IP protection and marketing rights etc.

Both large pharmaceutical companies, and small pharmaceutical companies can benefit from these early access-to-medicines schemes to bring innovative medicines to patients, often with an unmet need, more quickly (Total Orphan drugs, 2014) (Roland, 2014). Failing to obtain such exclusivity in comparison with competitors could influence market commercialization.

Comparators

Products can be submitted for market approval and reimbursement (necessary requisites for market access), but this submission needs to involve appropriate clinical comparators. These could be *direct comparators*, the current standard of care, or *indirect comparators*, competitive products under development in other pharmaceutical companies. Several products have no comparator products while others have many comparator products and need to show substantial added value to be taken in by the international market. Comparators for companies with a product in a highly competitive niche market may face a barrier for successful market commercialization.

Pricing

The pharmaceutical market can be distinguished from that of other industries along three pressing points (Kolassa, 2009):

1. Medicines are subject to derived demand. Medicines often need to be prescribed in response to a medical need. The use of the drug is determined by an essential decision maker and for prescription medicines, the prescriber is the physician who does not consume or pay for the medicine.
2. The prescription medicines can be perceived as 'negative goods,' as there are people who consume these who prefer not to.
3. Prescription medicines are considered to be experience goods. Their continuous use depends on positive experiences, and the actual utility can only be determined after usage (Kolassa, 1995) (Reisetter et al., 2005).

Factors that should be considered when pricing products are: the competitive landscape, proper company communication internally and externally about the patient, clinical and economic value of the therapy, the expected reimbursement and its environment, the company's abilities to act on potential payers responses on the product price and the public policy. As was briefly indicated, defining an appropriate price for products by small ventures and other pharmaceuticals desires in-depth knowledge of basic pricing principles, perception of value, role of pricing in medical decision making, role of reimbursement in pricing, competition and contracting basics. Small ventures often lack this knowledge and expertise and may perceive this as a barrier.

Reimbursement

It became clear in previous sections that providing appropriate evidence for the adoption of novel drugs or health care interventions is important to gain reimbursement or approval for coverage from national reimbursement or health technology agencies (Nooten, 2012) (Chambers & Neumann, 2010). Recent examples such as Xofigo or the products from the Dutch company Agendia (the MammaPrint) failed to gain reimbursement in several countries. If a product is to be funded or reimbursed by the payers, certain conditions before the market launch need to be met. Criteria for reimbursement vary

across countries but include several criteria such as cost-effectiveness, budget impact, drug price, unmet medical needs, safety and the effectiveness of the drug. Reimbursement decision makers assess value-based pricing to avoid products with no added value above current comparators. Furthermore, the value of the innovation has to be justified and the product's 'innovative character' value gains more attention (Morgen, 2008). Individual countries differ in their reimbursement process parameters, as can be seen in Figure 7.

TABLE 1

Important parameters in the reimbursement process in individual countries [30]

	Australia	Netherlands	Canada	France	Germany	Sweden	Italy	UK
Clinical effectiveness	✓	✓	✓	✓	✓	✓	✓	✓
Cost-effectiveness	✓	✓	✓	✓ (post-launch)	✓ (only in specific cases)	✓	✓	✓
Innovation[a]				✓			✓	

Note: Please note that this table was up-to-date at the time of submitting, however, things keep evolving within healthcare systems, which means this table might change over time.
[a] The term 'innovation' lacks specificity and differs by country. Only Italy has published criteria for identifying an innovative product [31]. With this algorithm, pharmaceuticals are designated as an important, moderate, or modest therapeutic innovation based on (i) the availability of existing products or (ii) the extent of the therapeutic benefit. In France, an improvement of medical benefit (ASMR) level (major innovation, important improvement, significant improvement, minor improvement and no improvement) is assigned for each product, but the criteria used to determine these levels is not defined by the Haute Autorité de Santé. Despite the potential for unclear or conflicting definitions of innovation, the value of demonstrating innovation remains high for reimbursement authorities.

Figure 7: Differences between reimbursement processes in individual countries (Nooten, 2012).

Larger companies as well as small ventures with less experience both struggle with identifying the appropriate requirements for evidence for reimbursement to achieve successful market access in different countries, something which becomes important in phase I and continues throughout the product life cycle. Clinical and economic evidence requirements remain key hurdles to commercialization (Faulkner et al., 2012).

5.2 The firm

Financial elements

Financial capital

In the long interval, before any income from commercial products, most small pharmaceutical ventures are dependent on support from external financial resources for their costs of development. Especially convincing narratives are necessary to assemble investments (Andersson et al., 2010) (Haslam et al., 2011).

In the first phases of the innovation process – when the investors face the greatest risk – external finance is partly absorbed by the public-sector subsidies and provisions. National subsidies in the Netherlands can be obtained from the CTMM, for example. Contemporary governments are however increasingly concerned with lowering their subsidy cost or purchasing a return on their investment.

Another source of funding are loans, such as bank loans or government innovation loans/credit. Recently, the government in the Netherlands decided to stimulate and strengthen the position of the small- and medium-sized firms and made 2,5 billion Euro available for these firms (HollandBIO, 2014).

During the development from early-stage basic research up to clinical trials, different funding channels are available such as subsidies, provisions, loans or credit. In the early stages, venture capitalists can also intermediate to raise investment for the development from, for example, pension funds, institutional investors or corporate ventures. Traditional VCs in the Netherlands are AescAp and IBTM. An organization could also strive to achieve initial public offering (IPO). In such a case, access is gained to the public market and a small venture is able to acquire additional capital and can invest in their own R&D.

Another alternative for funding is to plow back obtained revenues (from previous drugs in the market) and reinvest in the development of new products and broaden the company's product portfolio (Raaphorst, 2012).

External financial capital is necessary for small ventures that often lack the financial resources for the development of their product. Due to income from services or other 'cash cows,' small ventures may see the availability of financial capital as a barrier where others may not.

Lack of incentives like funds/grants for small ventures

To stimulate and fund these ventures, the pharmaceutical sector projects alongside venture capitalists, health funds invest approximately 125 million euros in R&D per year (Life Sciences & Health, 2011). In spite of these investments, acquiring sufficient financial capital is one the biggest challenges for entrepreneurs. The government has developed several methods to improve access to financial capital in the market. Large and small companies benefit, for example, from the WBSO and the innovation credit. The WBSO is the 'Wet Bevordering Speur- en Ontwikkelingswerk) that offers subsidies to lower the financial burden of R&D projects. The innovation credit, on the other hand, is credit available for innovative technical development projects. Next to these instruments, pre-seed-funds exist which are essential for projects in early phases of development.

The financial instruments contribute to the development of products but often have short running times or there is a low limit of height for these budgets. Small pharmaceutical ventures face difficulties in finding access to financial capital and this challenge may be a barrier for small ventures' international market access.

Risk sharing agreements

An alliance between a large pharmaceutical company and a small biotech firm could be seen as a win-win situation for both parties due to complementary needs and competencies, even though this sharing includes both parties' risks. Large pharmaceutical companies create strategic alliances with biotech firms for the development and commercialization of drugs to avoid taking all the risks involved in the development process of the drug. As these risks are highly significant, associated with a high chance of failure, and concern billion dollars of investment, alliances allow for 'wise' allocation of resources. Another consequence of partnering for large pharmaceuticals is the increased chance of strong pipeline potential drug products. Examples in the industry show that large pharmaceutical companies may focus on developing commercial drug candidates within key therapeutic areas in-house, while developing alliances with firms for the exploration of new target areas in which the company may not have expertise (Jackson, 2014). Many different collaboration types exist, see Table 2.

Table 2: Pharmaceutical alliances by deal types (Hughes et al., 2003)

Pharmaceutical alliances by deal types	
1. R&D and marketing-licensing	7. Product acquisition
2. Intra-Biotech	8. Product or technology swap
3. Marketing/Licensing	9. Reverse licensing
4. Incl. Equity	10. Joint venture
5. Co-promotion	11. Co-marketing
6. Incl. Royalty/profit split info	

Large pharmaceuticals are not the only players benefitting from collaboration, small biotech companies gain access to significant resources through such an alliance with a big pharma. The late-stage clinical trials demand high quantities of investment and without financing from a pharmaceutical partner, this would become very difficult. However, an IPO could also provide a solution for small biotech companies concerning such an issue.

The risk involved with an agreement is inherent to the drug development – the drug in development may fail along the development process. This situation can occur, but the risk is then born by both parties to the alliance. Such a risk is higher for small biotech firms as they will lose large R&D investments and a large portion of their market value. The risk will be less present for the large pharmaceutical companies due to the fact that these companies have numerous alliances and parallel in-house development processes.

Agreements create opportunities for small biotech firms, although risks and threats are also present. One of the risks for small biotech enterprises is that they will ultimately become acquired by the large pharmaceutical company. For a large pharmaceutical company, the alliance can be perceived as a 'trial period' in which they assess the drug candidates and should evidence appear promising, the large company could buy the small venture. Another risk for small biotech ventures may play out as follows; a large company strikes a deal to prevent competitors from accessing this new opportunity, making it more difficult for third parties to acquire the small biotech firm. This involves a high risk as the large partner may not have the intent to invest in rapid development of the drug and can heavily delay the process (Hughes et al., 2003). Making the partnerships work has achieved more attention in literature (Hughes et al., 2003) (Jackson, 2014).

Lack of experience of small ventures with market access or distribution may promt a collaboration with a big pharma. To find a proper partner and to make a favourable deal, could be a barrier for small ventures prior to international market access.

Network of the company

The embeddedness of small firms and social networks could provide opportunities and constraints to the actions of a company. Relational ties between firms allow for a flow of resources such as money, skills, information or social support. In this industry in particular, relations could support a company in conducting clinical trials, support for the regulatory approval process, manufacturing, marketing, distribution and sales (Powell et al., 1999). Today, the number of virtual biotech companies is rising. These virtual companies have a relatively low number of employees and outsource many activities such as preclinical and clinical trials. The lower the amount of fixed cost, the more money the company can invest in the development of new medicines. For these virtual companies, a network with skilled, specialized and experienced relations is highly important. The network of a company may influence the potential of a small venture to have a successful product launch.

Absorptive capacity

Absorptive capacity

In the current business environment more attention has been placed upon knowledge as a dominant source of competitive advantage. Firms must recognize or identify the value of external knowledge, and assimilate and apply it to commercial ends in the contemporary market environment. This capability of a firm is referred to as absorptive capacity (ACAP) (Cohen & Levinthal, Innovation and learning: The two faces of R&D, 1989) (Jansen & al., 2005). The development and the maintenance of ACAP is critical to a firm's long-term survival and success as it can reinforce, refocus or complement a company's knowledge base.

According to the Cohen and Levinthal research (1989), a company develops organizational knowledge about certain areas such as science and technology through its R&D activities, and strives

to understand how these areas relate to the company's products and market. This development describes the ability to identify and value external knowledge. Cohen and Levinthal (1990) also defined the ability to assimilate external knowledge as the ability of a company to facilitate knowledge sharing internally over time due to development of processes, procedures and policies in the company (Cohen & Levinthal, 1990). Finally, when a company becomes skilled enough to forecast technological trends, to create markets and products and to be able to maneuver strategically, this company has the ability to utilize external knowledge to its commercial ends.

Zahra and George (2002) broadened the ACAP dimensions of Cohen and Levinthal to four dimensions which play different but complementary roles: acquire, assimilate, transform and exploit. The first two elements are comprised in potential capacity and the latter two in realized capacity. Potential ACAP (PACAP) makes a firm receptive to acquiring and assimilating external knowledge but it does not guarantee exploitation while realized ACAP (RACAP) reflects a firm's capacity to leverage the absorbed knowledge. If a company needs to be able to cope with changes constantly, it requires both PACAP and RACAP since these have complementary roles (Zahra & George, 2002). Distinction between these two can allow research to study why some firms fail in cases of changes in the external environment while others survive under the same conditions. With this research, more insight in absorptive capacity regarding market access within the pharmaceutical industry will be attained.

Characteristics of absorptive capacity can be described related to three subjects, namely knowledge, organizational structure and organizational scope (Lane et al., 2006). Several literature studies focus on the characteristics of external knowledge that can influence assimilation or absorption of knowledge and other works draw attention to characteristics within an organization that underlie the absorptive capacity which could include management abilities see section *Management's abilities* later in this chapter. described later on. One of the characteristics concerning the subject of knowledge is the knowledge content or 'know-what'. Factors such as common skills, strategy and knowledge bases could enhance assimilation and absorption of knowledge (Bierly & Chakrabarti, 1996) (Lane & Lubatkin, 1998) (Ahuja & Katila, 2001) (Barkema & Vermeulen, 1998). The second characteristic of external knowledge is the 'tacitness'. If the knowledge exists of noncodifiable skills or implicit activities, the knowledge will be difficult to transfer to and be absorbed by - other companies (Saviottti, 1998) (Simonin, 1999) (Szulanskim, 1996). A third characteristic of knowledge is complexity. Simple knowledge is easier to absorb in comparison to complex knowledge (Simonin, 1999). For the aforementioned characteristics, however, there is lack of empirical evidence and they will as such not be considered in this study. Another element related to organizational learning is the effect of network position on innovation moderated by absorptive capacity. Tsai (2001) argues that network position results in augmented learning. This organizational learning element, however, is excluded from the research and will not be further discussed in this research study. In addition to these arguments stating that absorptive capacity results in assimilation of sought-after knowledge, the diversity of geographical experience that helps a company to develop knowledge structures in a new national setting (Barkema & Vermeulen, 1998) will be touched upon in *Management's abilities*. Some studies related to the last subject focusing on interorganizational learning suggest that interorganizational learning requires alliance partners that have sufficient knowledge similarity to provide learning and have enough knowledge dissimilarity to provide something worth learning (Lane & Lubatkin, 1998).

Most of the literature studies on absorptive capacity are limited to R&D related contexts, however, Lane (2006) mentioned that there should also be more studies on the role of absorptive capacity concerning the acquisition, assimilation, and commercial application of other types of business-related knowledge such as marketing expertise (Lane et al., 2001).

To measure absorptive capacity in this study, several factors such as age, size of the company, management team abilities including industry experience and international experience and employees abilities are considered and will be discussed below.

Age

Age suggests that older firms have a high absorptive capacity, as these companies have accumulated knowledge and have developed procedures and routines enabling assimilation of external knowledge. Literature on memory development suggests that accumulated prior knowledge could increase the ability to acquire knowledge and to recall this knowledge to use for commercial ends (Ahuja & Katila, 2001) (Kim, 1998) (Mowery et al., 1996).

Size

Mowery et al. 1996 have been arguing that the size of a company also plays a role in absorptive capacity. Large firms are likely to have accumulated knowledge and routines and have more resources to enhance their performance and innovation (Tsai, 2001).

Management's abilities

Some studies mention that the ability to evaluate and utilize external knowledge prior to related knowledge is valuable. This prior knowledge includes basic skills for managers but also knowledge on the most recent scientific and technological developments in a specific field. In addition, research on problem solving, particularly the studies of (Ellis, 1965) (Estes, 1970) (Bower & Hurry, 1993), argue that individual learning is the greatest when the new knowledge to be assimilated is related to the individual's existing knowledge structure. Therefore, the number of years of the management team's members suggests accumulation of prior knowledge and increases ability to acquire knowledge, to apply it and to use it for commercial ends. Furthermore, international experience of managers in several countries with different knowledge structures could contribute to the absorption, assimilation, application and the use of external knowledge.

Small pharmaceutical ventures with managers who have less (international) experience may face barriers in achieving international market access.

Employees' abilities

According to the Dutch Life Sciences and Health sector report of 2011, the Life Sciences and Health entrepreneurs indicate the difficulty of finding sufficient qualified personnel. Particularly employees with a background in Life Science and Health and with either a business, economic or technical degree are hard to find (Life Sciences and Health Sector, 2011) (Nyenrode Business University, 2009). They mention that the inflow of students is not sufficient enough.

Although skilled and trained employees may be difficult to find, human capital in small ventures is important. If employees of small ventures do not have the necessary skills, this may be a barrier for international market access.

Access to distribution network and promotion capacity

Lobbying

Effective lobbying focuses on target groups, in these cases scientific societies and national and regional politicians. Lobbying is a method, often informal, by which the actions of others could potentially be influenced to have a positive outcome. Lobbying, by branche organization on behalf of companies, will gain support of scientific societies and these societies can consequently transfer and stress the severity of the targeted disease and the added value, to public decision makers. The scientific societies generate pressure to stimulate market penetration of the new treatment. The scientific societies are seen as particularly useful as they can push to make expensive drugs informally and manage drug budget constraints. In the study of Jommi et al. 62 percent of the respondents (number of 21 companies in Italy) considers lobbying as an important aspect of market access. This suggests that lobbying may be a potential barrier to market access for small ventures.

Negotiating

In earlier stages, the scientists or the founders of the company must convince corporate and private investors (often venture capitalists) of the great potential of their product (Froud & al, 2006). Negotiation skills are very important during the establishment of collaboration agreements such as strategic alliances, joint ventures, licensing agreements or outsourcing (see also table 2), especially when it comes to concluding the best financial deal and best contract. To reach effective negotiation, managers must possess appropriate negotiation styles. Communication techniques are essential to effectively manage expectation, bargain for advantage, persuade and build on a consensus in which they can strive for win-win outcomes all the while maintaining trust, consistency and respect.

Creating awareness

Creating awareness about the added value of a product of a company essentially involves the education of society and patient-related organizations, but also includes tightening the relations with the target patient group. Companies need to get in contact with the patient societies and build upon a sustainable relationship and give free education to these societies to increase awareness among the public. Sometimes, patient organizations are highly well organized and others appear to be the opposite, having little time for new collaborations with a company.

Establishing relationships and increasing awareness among patients group's may indirectly effect decision makers (payers) and could contribute to alleviating the barriers to market access for small and big pharmaceutical companies.

5.3 The sector and market

Epidemiology

Market size

A company that strives to put its drugs on the market must address the best opportunities for the place to market the company's product. Epidemiological studies will help a company to investigate the markets that are the most interesting to target for a product. Products for rare diseases affect fewer than 200 000 patients (US) and these patients may be located worldwide. For these products, the market size is smaller in comparison to the market sizes of, for example, the diseases HIV and malaria. For a disease with a low number of patients, it is sometimes difficult to find patients for clinical trials making development more challenging. Orphan drugs with a relatively small market size can also face difficulties with appropriate pricing of the product. The development cost of the drug may have been extremely large and only a few patients will benefit from the drug making pricing and associated reimbursement challenging. Small ventures must be aware of the challenges or hurdles associated with the market size of their product as this may form a barrier to market entry.

Legislation

Strict national regulations in certain aspects

Research and development of new products for medical use can be restricted in several ways. Some governments, including that of the Dutch, have passed laws that prohibit all research on human embryos. However, some other countries endorse and even fund embryonic stem cell (ES) research. For ES research, the Netherlands as such has the Embryos Law of 2002 which put up restrictions banning human reproductive cloning and creation of hybrids and chimeras and regulates human ES cell research (The Witherspoon Council on Ethics and the Integrity of Science, 2012). Besides these restrictions, the Dutch government regulates the medical and scientific research done on children in the Netherlands. An independent committee in the Netherlands explored the associated ethical, legal medical, pharmalogical and psychological aspects of research possibilities with children and published recommendations for the government that restrict trials with children (Commisie Doek, 2009) (Nederlandse Vereniging voor Kindergeneeskunde, 2012).

Regulated national and international prescription guidelines

European pharmaceutical legislation regulates the pharmaceutical industry. Guidelines are present and can have implications for both large and small pharmaceutical companies. These regulations could pose challenges as the European Committee's advice on market authorization, medicinal products or their advice on prescription for first or second line treatments for the company's product could be less favorable than anticipated. Prescription guidelines may play a role for international market access.

Stakeholders

In the section *Changing market stakeholders' map*, the stakeholders were prescribed and in this section, the payers, patients and the key opinion leaders' influence will be briefly addressed.

Payers influence

The health care payer could be the government, the health insurer, employer or the patient (PriceWaterhouseCoopers, 2009). As aforementioned, the payers influence is strengthened due to the data-mining tools which they can use to analyze outcomes-based pricing and reimbursement schemes. Today, the payers asses the value of a pharmaceutical to their collective effect by balancing the clinical merits and the cost of a product. The payers are also highly interested in post-treatment data to define the ultimate effectiveness of the treatment and the realized clinical merits or the added value. Large and small pharmaceutical companies must educate the payers and explain the added value of their product by explaining the criticality, the unmet need and the number of alternatives. Payers can have an influence on reimbursement and may form a barrier for pharmaceutical companies' product market access.

Patients influence

Over the past years, patient involvement is strengthening due to mobile health technology and social media platforms. Patients can benefit from the latest developments allowing them to gain access to more information concerning drugs, treatments, long-term effects and are, by extension, capable of making value-based decisions. Patients can group together to lobby for the availability of several products and access to medicines by pressing for specific prescriptions. Small ventures and large pharmaceutical companies can profit from these lobbying patients and this group may play a role in market access.

Key opinion leaders' influence

Key opinion leaders in the pharmaceutical sector are hospital specialists or university professors engaged by the industry to provide advice on marketing a product and stimulate sales of new medicines. In different fields, the leading specialists are paid to influence different stakeholders of behalf of drug companies. These drug marketing strategies are used globally and described in the *Pharmaceutical Marketing* magazine as 'trick of the trade' (Moynihan, 2008). The marketing staff works with these Key Opinion Leaders to turn them into 'product champions' (Cook, 2001). Small ventures less experienced and with financial restrictions do not often have experiences in discussions with KOLs and this process could form a potential barrier for international market access.

HTA application

The increased use of HTA has been explained in the section *Augmented reliance on formal health technology assessment.* HTA is a rapidly evolving process that provides information for real-world decisions on the value of new and existing technologies. Today, the HTAs are more used for particular resource allocation decisions (Drummond et al., 2008). These include decisions on listing a drug on a national or local formulary, issuing a mandatory guidance on the use of technologies or describing the coverage for insurance plans. In the HTA, both the benefits and the costs of a product will be investigated and subsequently be provided to decision makers. HTA criteria and the implications differ

per country making launching a product in Europe with 28 countries difficult for small ventures without experience in this process.

5.4 Conceptual model

On the basis of the literature, a conceptual model has been developed and the model follows the micro-meso-marco framework that has been expounded in 2004 by Kurt Dopfer et al. (Christensen, 2012). The model allows for analysis of the coevolution between different forms of knowledge in an economic system and the context in which companies operate. It also considers the ability of the firm to adapt to changes in the environment and explains interplay between companies and a higher level of analysis including the study of industry sectors. The model, however, does not take into account the product factors which play an important role in the pharmaceutical sector: for example, the target product profile, value proposition including clinical value, patient value and economic value and specific exclusivity designations. Moreover, the meso and macro factors are closely intertwined and therefore these factors are combined in the sector-specific factors.

In the model, an overview of the relation scheme is provided. In this scheme, the dependent variable is perceived degree of difficulty of international market access and the independent factors are divided into three different groups: respectively, the product factors, the micro (firm specific) factors and the meso (sector specific) factors. The independent factors are assessed by construct factors and can be found in *Appendix F: Conceptual model construct factors*.

The lines connecting the different levels of product, firm and sector illustrate a potential correlation between the levels and mutual interaction.

The same accounts for the links between the factors for product, firm and sector level and market access. The product level factors are related to products in the pharmaceutical industry which must go through clinical trial phases, as is the case with, for example, therapeutical medicines. The firm specific factors focus on firms within the pharmaceutical sector with products that must be tested in clinical phases, therefore no pharmaceutical suppliers of research discovery tools and assays are taken into account. The sector specific factors are related to the pharmaceutical industry.

The conceptual model can be seen in figure 8.

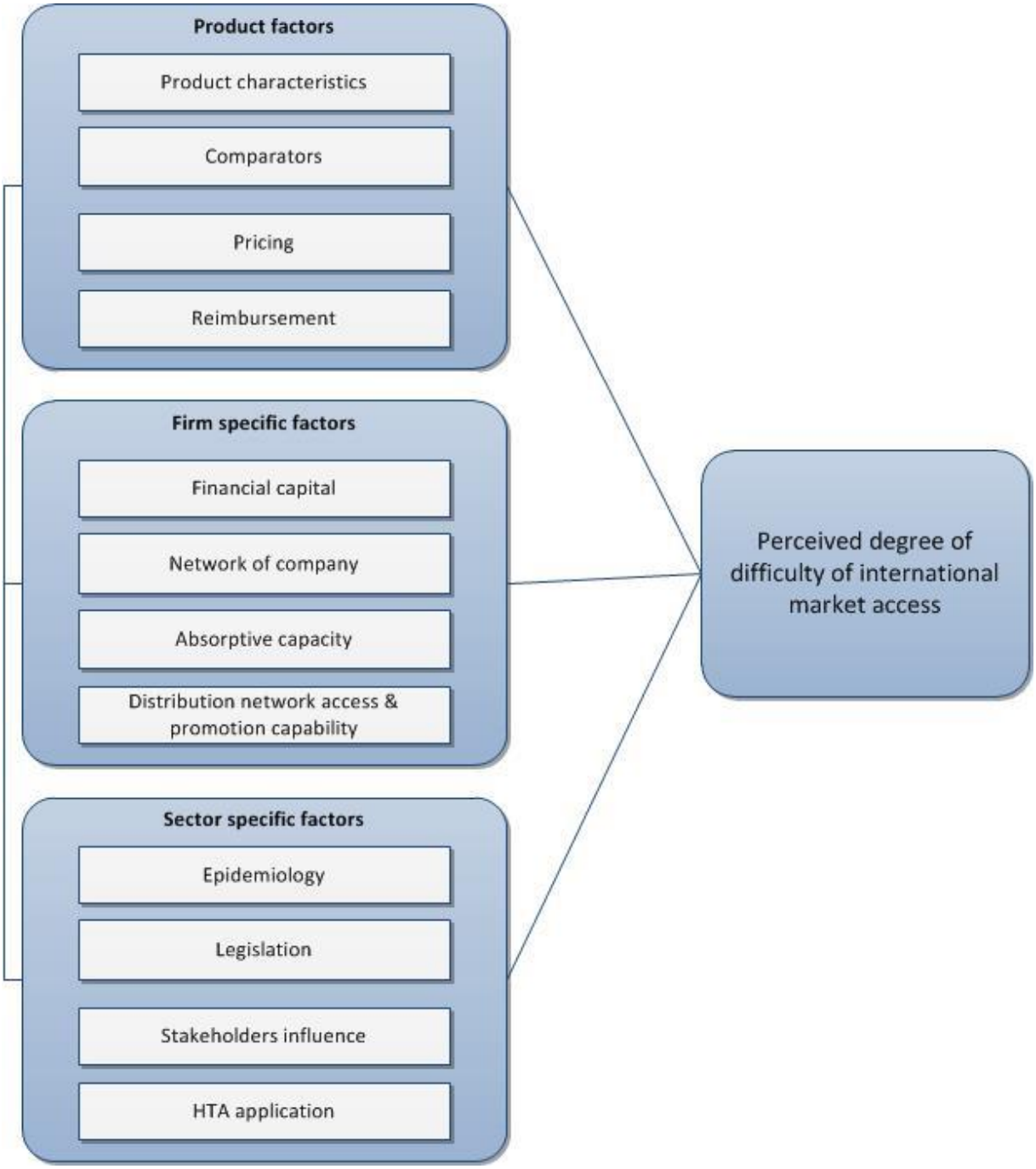


Figure 8: Conceptual model of the factors influencing the perceived degree of international market access:

5.5 Summary and conclusions

The potential factors provided may be barriers of international market access. At each of the three different levels, will these factors be analyzed by means of quantitative and qualitative research to assess their importance and gravity. From these analyses, it can be determined which of the critical factors form barriers and have influence on international market access and must be included or excluded during the design of the decision-support tool. This study will give more clarification factors in the conceptual model.

6. METHODOLOGY

In this section the methodology of this study which aims to increase the understanding of critical factors of market access and to develop a decision-support tool particularly for small ventures will be discussed. The methodology concerns the database collection, the online survey, (expert) interviews, model estimation, rough set data analysis, decision-support tool design and validation of the tool.

6.1 Data collection

A database with Dutch life sciences and health companies was generated in order to define a proper population and sample for this study. To form a proper database an explorative desk study was performed to collect information on life sciences and health companies in the Netherlands. The companies and data on the companies was obtained by consulting Life Sciences at work site and document, LinkedIn, search engine Google, database of Laurens Klomp, additional information employees of the company to-BBB, the database Globaldata, the database of BioSciencePark, HollandBio website and a database of Lonneke Baas. An overview of the companies and several institutes was generated consisting of 489 life sciences and health related organizations. After the generation of the list of life sciences and health companies in the Netherlands 51 small to medium sized ventures (up to 150 employees) were selected. Companies products phases can range from the discovery up to marketed. Only the companies with products that need to encounter clinical trials were selected.

Selected sample

The selected sample of respondents for the online survey was obtained from the generated database. When the database was generated approximately fifty small ventures were selected. This sample of the companies existed of small ventures with drugs ranging from the discovery phase up to marketed products. The companies selected had to have products that need to encounter clinical trials. The selection was based on *proportionate stratified random sampling*. The database of companies was divided in meaningful segments. First the pharmaceutical product developing companies were chosen and afterwards from this selection the product developing companies that have to encounter clinical trials were selected. Then from this last sample set of companies contact information was collected by using the Google search engine, the company websites and company documents. The online survey required senior managers in the industry and therefore the managers of the same level, C-level, were the *unit of analysis*. This contributed to the challenges in to persuade and convince them to participate in this study due to priorities and busy schedules. The senior managers were invited by e-mail via the online tool Qualtrics.com to fill in the online survey via a link.

Online survey

Design online survey

A questionnaire for the survey was developed to identify the importance and the gravity of several market access barriers, to explore how international market access is perceived (easy vs problematic). With this data, the factors playing a role prior to access will be collected and will be included in the tool. In addition the explanatory power of the barriers towards the perceived degree of difficulty of international market access will be assessed. The barriers with the highest frequencies will be emphasized in the decision-support tool as highly important to consider. Solution and information on the barriers for small ventures in the pharmaceutical industry will also be provided.

A survey was chosen over conducting interviews because the tool of interest quantitative data would be desired. It is assumed that the best results would be obtained when assessing the barriers by an online survey. During the development of the questionnaire several elements were considered such as the number of questions, the relevance of the questions, wording and the language of the questions,

the sequencing of the questions and the classification of data and personal information of the senior managers.

The developed questionnaire consisted of a short introduction followed by ten questions in total. The questions were developed based on the information obtained from the literature review and the conceptual framework was based on three groups product, company and sector specific factors. The suvey questions addressed first general questions and characteristics and secondly specific information to obtain senior managers perspectives. Several of the general questions were acquired from previous interviews from the Spin-Up study performed by Prof. M. van Geenhuizen, Technology Policy and Management, Delft University of Technology, related to the subjects of full time equivalent and turnover of the company. Additionally, open questions were included focusing on collecting new and diversified information on the main products of the company and associated barriers and solutions for market access.

Expert interview and online survey testing

An expert interview was performed to identify the gravity of several market access barriers and to assess possible missing or redundant barriers.

Afterwards a pilot version was trialed with two different persons within a small pharmaceutical venture. This testing was done to test the usability and the intelligibility and led to several modifications with respect to the rephrasing of questions and to avoid misinterpretations.

Performance online survey

The analysis of the quantitative and qualitative data gathered by the online led to results for this study with an explorative character. Unfortunately the survey response so the short MABS survey was low (n=4) which led to follow up in-depth interviews.

The questionnaire used in this study was first designed and then transformed into an on-line survey with Qualtrics.com named *Market Access Barriers and Strategies (MABS survey 2014 TU Delft, Technology, Policy and Management* and can be found in *Appendix I1: MABS survey***.** The survey could be completed in fifteen minutes and was developed in English. The online survey could be completed during 12 working days (21st of May – 6th of June, 2014). The time of the year in which the survey was mailed could have contributed to the low response rate.

In total 16 out of 53 opened the e-mail with the online survey link. Only two respondents finished the survey. Therefore the response of the survey was too low and additional interviews were needed to identify among other things the importance and the gravity of several market access barriers, to explore how market access is perceived.

After low response a short version of the MABS survey was created and sent by e-mail to the same companies. This short version excludes several general questions and only focuses on the gravity of market barriers. For a more detailed view have a look at *Appendix I2:Short version of the MABS survey*.

Company interviews

Interviews were performed to collected more data. Companies' respondents had to identify the importance and the gravity of several market access barriers.. The outline of the interview questions was similar to the online survey except for question one which was eliminated as the job function of the interviewees was already clear. The survey was shortened during the interview process after (expert & company) interviews and after acquirement of progressive insight. Both the survey and the interviews allowed scores (on a five-point scale for the gravity of the barriers) to be made in a standardized way and the interviews allowed in addition for more in-depth insights.

Respondent sample

From the population of fifty companies, a sample of eighteen companies was selected based on differentiating factors (this sample of companies excluded the companies that had responded to the survey). The differentiating factors selected were: the age of the company, the number of employees, the phases of the company's products, the indication of company's products (focus on orphan diseases) and the funding type. Based on these differentiating factors identified, companies were selected. Some of senior managers of these fifteen selected companies were contacted by Prof. dr. Marina van Geenhuizen, Economics of Technology and Innovation, Faculty of Technology, Policy and Management Delft University of Technology for a face-to-face interview. Besides these senior managers several experts with more than 25 years of experiences in the Life sciences and health industry were contacted. In the sample two cases were added by means of triangulation. *Triangulation* was performed to achieve a higher number of companies in the sample.

To conclude data was obtained by means of:

- MABS survey N=2
- MABS short survey N=4
- In-depth interviews N=6
- Triangulation N=2

Biases in data

The survey and interviews results may be influenced by some factors that could lead to biases in the data. Biases could be due to:

- *Non-response*. A failure to obtain information from a number of participants included in the sample may lead to the non-response error. This error exists to the extent that those who did respond to the survey are different from those who did not. The non-respondents may not have responded because they were not at work (on holiday or illness) or they refused to respond. The survey was sent several times so the first incidence, not at work, was reduced. The rate of refusals depends on for example the length of the survey. The survey was shortened which led to 4 more responses of companies in the sample. Refusal could also be related to the data collection method. The first time the data was collected by means of an online survey, the second time (the short survey) was sent by e-mail and therefore this incidence was taken into account. After the survey additional personal interviews were performed which improved the return rate. Another reason for refusal is the patronage of the research. Several questions involved highly specific (confidential) information of the company which could have triggered refusal (Sekaran & Bougie, 2010).
- *The method of self-estimation*. In this research respondents were asked to compare their company to an average or generalized other companies. (respondents could have compared their company with competitive companies or with other companies in their branche) The majority of the of the persons rate their company as superior to other companies. Judgments about the 'average company' are not an appropriate baseline for assessing bias in self-evaluation (Gramzow et al., 2003). Some respondents may exaggerate their true standing and this method therefore may influence the obtained data.

6.2 Model estimation

The interviews with experts in the industry and interviews with senior managers of different companies in the industry provided valuable insights and which has led to the reduction of potential factors for market access barriers in subsequent interviews with senior managers within the industry. Several potential factors were eliminated for the RSDA as these would make the analysis less useful. The factors eliminated will be described in section 7 *Results model estimation*.

Rough Set Data Analysis (RSDA)

Data gathered from the companies was used to develop and information table. This table was the basis for the systematic analysis, the Rough Set Data Analysis (RSDA).

A modular software system Rough Set Data Explorer (ROSE) was used in this study. The software created at the Laboratory of Intelligent Decision-support Systems of the Institute of Computing Science in Poznan by Predki, Slowinski and Stefanowski in 1998 is a user-friendly software to apply RSDA. Some other software programs were created like ROSETTA however ROSE is most user-friendly. ROSE was used as a 'causal approach' to produce a set of decision rules on the occurrence of market access barriers. The rules and outcomes were used to assess implications concerning perceived difficulty of international market access. With this software the aim was to derive general testable propositions from a limited number of cases. This program was applied because RSDA fits an analysis type of small samples, low levels of measurement of data (i.e. categorical) and the 'fuzzy' character of the data (Pawlak, Rough Sets, 1991) (Pawlak, 2001). In RSDA an assumption can be made about the data, namely the value of the determining factors can be categorized. This is the main advantage of RSDA in comparison with more conventional methods like multiple regression analysis and discrete choice models.

The data was collected in an information table, a matrix in which rows are labeled by *objects* and the companies and the columns are labeled by *attributes* in this case being the potential market access barriers *factors*. The objects are arranged on the basis of their condition attributes (C) and decision attribute (D). The two types of attributes are analogous to the independent factors (the potential barriers) and the dependent variable (perceived degree of difficulty of international market access) of conventional regression analysis (Van Geenhuizen & Nijkamp, 2012). With this data RSDA was performed.

In the application of the Rough Set Data Analysis main steps based on the rough set theory had to be carried out (Gülümser & Nijkamp, 2009). One of the steps is, pre-processing, the quality of the classification of the decision attributes was made visible. In the following step, attribute reduction was used to form all combination of condition attributes that was able to determine the variation in the decision attribute without the need of another condition. The last step is rule induction which generates *decision rules*, that are composed on the basis of the information table. The decision rules are presented in a 'IF *condition* THEN decision' format. The strength of the decision rules is measured by the *coverage*. These rules show trends or logic rules from the fuzzy data.

6.3 Decision-support tool

Development

The RSDA was used to assess the explanatory power of several factors. Factors that influence the perceived degree of difficulty of international market access are considered during the tool design.
The development of the decision-support tool consisted of different phases. The checklist was first developed according to the requirements for checklists (e.g. concise objectives, actionable) and the specific criteria for a market access checklist (e.g. anticipated on heterogeneity and change in the market). More details on the development criteria can be found in section 8. Subsequently the checklist was drafted in which the outlook was taken into account. After these phases the checklist was validated against two experienced persons in the industry.

Validation of tool

The validity of the proposed decision-support tool was tested by means of validation interviews with experts (different from the first expert) in the industry related to a Venture Capitalist and small venture (a company within the selected sample). Validation with these expert had to done before the checklist could be used as a decision-making support tool within small ventures.

7. RESULTS

In this section the results on the emperical study will discussed in detail and concerns the results of the database collection, the online surveys, (expert) interviews, model estimation, rough set data analysis, decision-support tool design and validation of the tool.

7.1 Characteristics of the population

Subsequently a selection was made for small ventures with drugs ranging from the discovery phase up to marketed products. The companies of the selected sample had to have products that need to encounter clinical trials. In total 51 companies matched this selection criteria and upon request the selection of companies can be provided.

Size and age

The size of the selected Dutch companies participating in this study was analyzed to determine the mean, the percentages, the SD of the size of the companies. The companies were divided in three groups divided into *micro* with 1 to 10 employees, *small* has 11 to 50 employees, *medium* has 51-200 employees. The M_{size} = 1.69 and the frequencies and the percentages of the total were respectively 23, 21, 7 and 45.1, 41.2 and 13.7 which can be found in Table 3. The results for the ages of the participating companies were N=51, M_{age} = 8.51, SD_{age} = 8.391 and the range ways from 1 to 55 years.

Phases of product development and type of product

The selected companies could have products in different phase of the company such as Discovery, Phase I, Phase II, Phase III, Regulatory review, Phase IV and market. The percentages the for companies in a specific phase was determined can be found in Table 3.

The set of selected companies were divided by the type of product in namely *orphan drugs* or *non-orphan drugs*. Out of the 51 companies 16 companies had orphan disease targeted rugs and 35 had non-orphan drug focused products, therefore the $M_{type\ of\ product}$ = 1.69.

Cash cows

Several companies have products market and others have sides activities such as delivering services to obtain and inflow of cash. In this case 12 out of 51 companies have cash cows with an associated percentage of 23.5.

Table 3: Summary of the characteristics of the population.; the amount of companies and the associated percentage of total are shown

		N	Percentage of total
Size of the company	Micro	23	45,1
	Small	21	41,2
	Medium	7	13,7
Phase	Discovery	42	82,4
	Phase I	15	29,4
	Phase II	19	37,3
	Phase III	7	13,7
	Regulatory review	1	2,0
	Phase IV	1	2,0
	Marketed	4	7,4
Product type	Orphan drug	16	31,4
	Non-orphan drugs	35	68,6
Cash cows	Cash cow	12	25,5
	No cash cow	39	76,5

7.2 Results of respondents and conclusions

In this section the results of the fourteen respondents form the selected sample, derived from the population of 51 companies, will be described and discussed. Several in-dept anonymous interviews with experts and companies were performed and the upon request insight can be gained in the interview results.

Respondent characteristics

Job description, job field and amount of years in company

The respondents that participated on behalf of the company were all senior managers such as Chief Executive Officer, Chief Commercial Officer or Chief Business Officer. This was important for consistency in the responses towards the potential market access barriers. The amount of time these senior managers worked in the company ranged from one year up fourteen years.
As many of these senior managers have around 25 years of experience in the industry (see *Experience of the management team*) it can be seen that they have been shifting between companies lately.

From the characteristics of the managers it can be seen that managers in C-level positions often shift between companies and do not stay at a company for many years but do remain in the pharmaceutical and biotechnology industry.

Characteristics of the respondents' companies

The respondents of the survey and the interviews are combined and a description of their size, age, product phase and product type will be provided. In total 14 companies participated in the study. An overview of the coding and more detailed information and graphs can be found in *Appendix J: Characteristics of respondents.*

Size, network type and age

The respondents from the survey and interviews were grouped in micro, small and medium. The M_{size} = 1.64 and the frequencies and the percentages can be found in Table 4. The size of the companies is not directly correlated with the main product phase of the company as companies outsource activities and accordingly could have low fte in a later development phase. Several companies are virtual companies and have a different network type than other companies in the sample. 6 out of fourteen companies are virtual companies.

Then the results for the ages of the participating companies were M_{age} = 6.71 year, SD_{age} =5.090 and the range ways from 1 to 16 years.

Turnover, cash cows and funding

The results show that 53.8 percent of the companies had the lowest turnover (below 100.000 euro) while 15.4 percent had a turnover of between 100.001-500.000, as well two companies had a turnover of 1.000.001-5.000.000 (14. Percent) and two companies had a turnover of 'more' (15.4 percent). The turnover, however, is difficult to define and more will be discussed in the section *Discussion*.

Several companies have already products marketed and others have sides activities such as delivering services to obtain and inflow of cash. In this sample 2 out of 14 companies have cash cows from a marketed product or strategic alliance. Cash cows will not be included in the analysis due to the difference interpretations of managers which have to be controlled.

Also funding types were analyzed. The sample selection contained 7 companies with financing rounds, 2 companies that pulled an IPO and 5 companies with neither of these two funding types.
Funding has to be attracted to execute research or development of a product. Often companies use seed financing in the preclinical phase and even sometimes in phase I. But to perform a phase II study Venture Capital or a collaboration is needed to finance the studies. For the phase III study often a large

amount of investments are necessary and companies a destined to collaborate with a big company or have to make an IPO to perform this highly expensive study. As can be seen in Table 4 the two companies had made an IPO (mid-2013 and the start-2014) have their main product in phase III and in the regulatory review phase.

Phases of the company and main product type

The selected companies could have products in different phase of the company such as Discovery, Phase I, Phase II, Phase III, Regulatory review, Phase IV and market. The percentages for the companies in a specific phase was determined. The numbers and the associated percentage can be seen in Table 4. Only four out of 14 are solely in the discovery phase while the other companies have a product in clinical trial phases or have already gone through these phases.

It is noteworthy to mention that company E has inlicensed their product from a larger company after the preclinical phase and phase I and did have to encounter early phases.

Product type

The set of selected companies were divided by the type of product in namely *orphan drugs* or *non-orphan drugs*. Out of the 14 companies 5 companies had orphan disease targeted rugs and 9 had non-orphan drug focused products, therefore the $M_{\text{type of product}} = 1.64$.

Of this sample 35.7 percent of the companies focuses on orphan drugs for rare diseases. Several of these companies have an orphan drug status (Breakthrough designation) for their main product. One company in the sample, has the potential to follow the strategy as an orphan drug with less clinical trials but it will only follow this path if a general study is not feasible due to the lack of investment or lack of a partnership.

The respondents could also be divided by gene therapy and non-gene therapy with respectively the following percentages 7,1 and 92,9. Gene therapy product companies face difficulties due to the 'newness' of product in the industry as no gene therapy product exist in the marketplace yet.

Several of these companies developed platform technologies which may influence their turnover. However these differences in product type are not taken into account in this study.

Indications of the main product's of per company

It can be seen that the focus of indications of the companies highly differs some examples are CNS, Multiple sclerosis, oncology indications, depression, dyslipidemia and health aging. Several companies indicated more than one target indication of their product. Today, companies target multiple diseases as medicine may improve the conditions of other disease as well. Therefore more indications for one product can exist. Often companies target first one indication and perform clinical I to test for this indication. In the next phase however a company can decide to switch to another indication for further clinical studies. If a company wants to target several indications more studies are necessary and these are involved with more money which in unfavorable for small ventures with limited resources. Strategic decisions to decide what the target indication will be is important and this decision could be influenced by Key Opinion Leaders according to one of the respondents.

Table 4: Overview of the respondents for the interviews, the number and percentages for the size, phase, prodcut type, cash cow and funding types

		N	Percentage
	Micro	8	57,1
	Small	3	21,4
Size of the company	Medium	3	21,4
	Virtual firm	6	42,9
Network type	Non-virtual firm	8	57,1
	<100.000	7	53,8
	100.001-500.000	2	15,4
	1.000.001-5.000.000	2	15,4
Turnover class	More	2	15,4
	Discovery	10	71,4
	Phase I	5	35,7
	Phase II	7	50,0
	Phase III	3	21,4
	Regulatory review	2	14,3
	Phase IV	0	0
Phase	Marketed	1	7,1
	Orphan drug	5	35,7
	Non-orphan drugs	9	64,3
	Gene therapy	1	7,1
Product type	Non-gene therapy	13	92,9
	Cash cow	2	14,3
Cash cows	No cash cow	12	85,7
	Financing rounds VC	7	50,0
	IPO	2	14,3
Funding types	Neither of them	5	35,7

Management teams

In Table 5 an overview of the management team experiences of the companies in the sample are provided.

Table 5: Summary of company's management team members and their (international) experiences

Company B	-	One MT with
	-	International project experience and project leader experience within a large company
Company E	-	Four MT
	-	Management team has members with members that have over 20 years experience in the industry in sales, marketing, business development and general management.
	-	The management contains a member which has published over 500 research papers
Company K	-	Eight MT
	-	Management team has experience with national and international settings and with a CRO, IPO and an acquisition. Members with over 25 years of experience in the industry in commercial roles
	-	Experience with international operational and supply chain, relocation of activities and manufacturing.

It can be concluded that most of the companies with a product in a later stage of the development have senior managers with many years of international working experiences.
From this data it can be seen most of the managers have a background in biomedical sciences, pharmacy, medical sciences and chemistry or specifically in finance.

Additionally, some companies in the sample have specialist in the management team with operating and supply chain experiences. The presence of these members, however, is strongly related to the business model of the company. Companies can produce and manufacture the product in-house or can make an agreement with a partner to manufacture. Other companies may desire to be acquired or strive for a buyout and do not focus on manufacturing or operational activities.

For companies that have made an IPO the management team has namely around ten members in the team and some of these members have many years of international experience. The management teams of the other companies also pulled financing rounds and achieved investments. The management team has to have experienced management team members with a track record to attract investments from venture capitalists. It is noteworthy that some management teams include managers that work parttime for the company as 'consultants'.

Market access

Descriptions of the main problem/challenge of the companies

The initial perspectives on the main problem or challenge for the company product's market access were derived. The managers indicated that financial funding is often a challenge for companies. Also convincing data and narratives on the added value of the product and the innovativeness to potential (big) partners, venture capitalists and authorities is perceived as a challenge. Lastly the political barriers or bureaucracy are mentioned and non-harmonized regulations are perceived as problems by the senior managers of these companies.

Degree of difficulty of market access

To measure the dependent variable, the senior managers' perceived market access perspective had to be quantified by choosing between *very problematic*, *problematic*, *neutral*, *easy* and *very easy*. From the research it appears that 21.4 percent perceives market access as very problematic, 42.9 percent perceives market access as problematic, 28.6 companies believe that market access is neutral and only 1 company perceives market access as easy with 7.1 percent. The $M_{\text{market access}} = 2.21$.

Gravity of the barriers to market access

Initially the importance and the gravity of the independent factors, the market access barriers were measured. However due to the low response the survey was adjusted to a short version of the MABS survey. Due to this only the gravity of the potential barriers was measured. Moreover list of potential barriers was narrowed down to sixteen potential barriers after various (expert) interviews and gained insight. Only the results of the responses to the sixteen factors, the potential barriers will elaborated on in this section. The potential barriers are coded from A1-A16 and the codes are shown in Table 6.

Table 6: Coding of the independent factors, the potential barriers to international market access

Number	Potential barrier to international market access
A1	Meet the target product profile requirements for clinical usage such as dosage, safety, side effects, quality of life
A2	Currently on the market medicines (direct comparators)
A3	Define appropriate pricing
A4	Meet the reimbursement requirements
A5	Effective negotiation
A6	Creating awareness (e.g. patients societies)
A7	Availability of financial capital
A8	Lack of risk-sharing agreements
A9	Management team abilities
A10	Too strict national regulations in certain aspects
A11	Lack of financial incentives such as funds/grants (e.g. Innovation credit)
A12	Too regulated national or international guidelines
A13	Payers influence
A14	Patients influence (excluding payers)
A15	Key Opinion Leader's influence
A16	Meet the Health Technology Assessment (if required)

The gravity of the barrier to market access runs from 1 to 5. Number 1 in this indicates very small gravity of the potential barrier and 5 indicates a very large gravity. The numbers 9, 10 and 11 are as well included respectively: not available as these are not considered yet, not available as it the variable is not relevant, not available as it is not known. The rankings per company per potential barrier can be seen it Table 7.

Table 7: Rankings per company per potential barrier[b] to international market access

Objects[a]	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16
B	9	9	9	9	4	9	4	4	4	9	4	9	9	9	9	9
E	3	3	2	4	2	2	5	4	1	3	1	1	4	1	3	4
K	5	1	5	5	1	1	3	1	1	1	1	1	5	3	5	5

[a] Objects B, E and K are companies. [b] A1-A16 are potential barriers (factors)

The numbers 9, 10 and 11 were included as some companies in the sample did not respond to all the questions. In some cases the respondents did not answer a question because a potential barrier is 'too far to be considered' or due to the fact that some of the potential barriers were 'not relevant' or lastly because the respondents did 'not know' how to rank the potential barrier.

Some rankings per company will be discussed shortly and more detailed information data could be provided upon request.

- Company B

Company B with its main product in the discovery phase, did not fully answer the questions on the potential market access barriers because 'the potential barriers are too far to consider'.

- Company E

The respondent of this company argues TPP requirements are highly important but do not form a large barrier to market access. A missing potential barrier that could be added, is upscaling. The company has two indirect comparators, both of them are already in the next stage of development, but the products of large pharmaceutical companies do not treat the company because company's product has advantages over the comparators. Among the factors that received a high gravity were the availability of financial capital and the lack of agreements. Phase III has to be execute and investments or an agreements is necessary to continue. Appropriate pricing received a low score on gravity of barrier to market access due to the fact that this market is already developed and benchmarking will be done to

predict the price of the product. The management abilities were ranked as a very small gravity of the barrier because the management is highly experienced and has a track record.

- Company K

Company K has a very unique product which results in difficulties with appropriate pricing and reimbursement and therefore these received a high score. Financial capital is not a barrier as the company made an IPO. Also the management team abilities and effective negotiation were ranked low as these currently do not form a large barrier. A missing variable 'advocacy development' was stressed to be very large barrier for the company. Education of persons in the world who understand the product and the business perspective is important. In addition the respondent draw attention to patient diagnostics and screening infrastructure in each market. The company highlighted as well the non-harmonized regulations with implications for reimbursement, pricing and HTA and these potential barriers gained a very large gravity to international market access.

Most pressing barriers

After discussing the potential factors for market access and their gravity the companies respondents were asked again to define the most pressing barriers related to market access for their company. It appeared that 8 out of 14 companies mentioned financing/funding and financial incentives. The reason why the other companies did not indicate financing as a barriers was because other companies had made a IPO recently or recently closed a successful financing round. Convincing data (efficiency), pricing and reimbursement, HTA and regulations are as well all mentioned several times.

Suggestions for pressing barriers

Only by several companies solutions for the barriers were mentioned and will be described below.

- Build upon a virtual network, that includes outsourcing of many activities and make sure that proper management abilities and access to business and scientific networks is present. Strictly focus on the company's goal and create backup plans in case agreements or collaborations do not work out.
- Be aware of dependent and independent timelines. Dependent timelines a company can control and can influence these timelines while other timelines cannot be controlled. A timeline a company cannot control is how long authorities need to and understand the need for a new drug and price and reimbursement and how to assess it.
- A company should as result not make promises internally or externally (investors) on specific dates or periods for the launch of a product in a specific country. A company can mention that it will try and apply for pricing and reimbursement in specific period but the results nor the time of approval by the authorities cannot be influenced.
- In this industry there should be a much stronger alignment between medical need and the pricing and reimbursement. There should be willingness to speed up the process. When physicians would say that there is an absolute need for this product, then authorities should give priority to this product. The medical need should be put much more in the front than the question if the medicine or treatment is affordable.
- Bring all the stakeholders together and this will alleviate the barriers to market access. Companies have to start as well development programs with multiple TPPs/trial indications to overcome TPP as a barrier.
- Companies need to gain insight in market access to understand valuation and this can support discussions to acquire more funding.

In sum, the respondent provided solution at firm level and at policy level. The firm level solutions concern strategy, the involvement of KOLs in the development, awareness of independent timelines.

7.3. Model estimation and Rough Set Data Analyses

Factors and measurement RSDA1

The data derived from the survey, the interviews and triangulation allowed scores to be made in a standardized way and were used to perform RSDA. The analysis was used as a causal approach to find causalities between the market access barriers and the perceived international market access barriers. The results from the analysis add to the verification of the proposed conceptual model and can explained the strength of the different factors (the higher frequency of an attribute the stronger is the explanatory power).

The gathered data could be divided under two headings namely the *characteristic information* of the companies and the *market access information*. The characteristic information that was collected was in terms of the size, the age, the product phases, the product type, cash cow and the funding type. The market access information was bases upon the factors C1-C16.

For the purpose of the Rough Set Data Analysis some of the characteristic factors and some of the market access factors were removed. To narrow down the list of factors, specifically the responses of the potential barriers to market access were assessed and accordingly the factors with the most contrasting results were selected. The variable *Effective negotiation* for instance, often highly ranked, was removed for the RSDA. The decision attribute (D) was the perceived degree of difficulty of international market access for the company and the condition attributes are the potential barriers (C). The attributes are described in Table 8.

Table 8: Explanation of the factors for RSDA

Name	Explanation	Category
Characteristic information		
C1: Size	Number of employees/fte of the company	Catergorical: 1 = 0-10 employees, 2= 11-50 employees, 3= 51 or more employees
C2: Product type	Orphan or non-orphan product	Dummy: 1= orphan product, 2= non-orphan product
Market access information		
C3: TPP	Target product profile requirements	Categorical: 1= small gravity, 2= neutral gravity, 3 =large gravity, 9= not available as these are not considered yet, 10= not available as the variable is not relevant, 11= not available as it is not known
C4: Pricing	Appropriate pricing	
C5: Reimbursement	Reimbursement requirements	
C6: Creating awareness	Creating awareness	
C7: Financial capital	Availability of financial capital	
C8: Management	Management abilities	
C9: Regulations	Too strict regulations	
C10: Agreements	Lack of risk sharing agreements	
D: Market access	Degree of difficulty of international market access	Categorical: 1=very problematic, 2= problematic, 3= neutral, 4= easy, 5= very easy

The data representation is categorical for all the attributes except for product type which is dummy (1= orphan, 2= non orphan). The conditional attributes' perceived gravity was measured by using stated preference and a five-point scale. A three-class classification was consequently adopted because a refined classification would have resulted in a less useful rough set analysis.

In addition the product type of the company's product was categorized by orphan and non-orphan product (binary coding). Only the variable size was categorized into three categories namely 0-10 employees, 11-50 employees and 51 and more employees. An example of the information table can be seen in Table 9.

Table 9: Structure of the infromation table (illustrated by three companies)[a]

Objects[b]	C1	C2	C3	C4	C5	C6	C7	C8	C9	D
B	1	2	9	9	9	9	3	3	9	4
C	1	2	3	1	3	1	3	3	1	3
D	2	1	3	1	1	3	3	2	1	4

[a] C1-C9: the condition attributes. [b] B-D: case studies (companies).

This information table served as the basis for the RSDA. In pre-processing steps the quality and the accuracy of each of the condition attributes C1-C9 of the decision attribute were assessed. The accuracy of classification has to be 1 otherwise the data and companies in the sample are not fully unambiguous concerning their allocation to the categories of the decision attribute (1=very problematic, 2= problematic, 3= neutral, 4= easy, 5= very easy). In *Appendix: RSDA1 approximations, frequencies of attributes and the core attribute*, the approximation of the rough set data is shown.

In the interpretation of the rough set results the frequencies, of which a particular condition attributes occur in the set of rules, was looked at. The higher the frequency of a condition attribute, the stronger is the explanatory power of that attribute. The condition attributes with the highest frequencies are the TPP requirements, management team and the risk sharing agreements (respectively 51.35, 56.76 and 70.27 percent).

Also the coverage of each rule was used to interpret the data. *Coverage* is the an indicator of the strength of the rules. The coverage is calculated as the number of cases with a similar set of attributes and a score on the decision attribute as a percentage as a percentage share of all cases with this score on the decision attribute. The highest level of coverage in the analysis was 14.3% (2/12) but most did not exceed 7.1% (1/14). Often the coverage does exceed 50% in other rough set analyses.

Shaping factors of the perceived degree of difficulty of international market access

It can be seen that on the basis of the selected factors and with the application of the RSDA eleven decision rules where obtained which explain the different levels of perceived difficulty of international market access. All the rules will be taken into account because and no rules exclude other rules. Both market access factors and characteristic factors, particularly product type, have impact on the determination of perceived degree of difficulty of international market access.

When the condition attributes in the decision rules are considered two attributes had a relatively strong power. The attributes management team abilities and reimbursement requirements, occurred 5 and 4 times in the decision rules. The frequencies of the condition attributes can be seen in *Appendix K: Results of the rough set analysis*, and can support the conceptual model.

From the analysis it could be seen that rule 3, 4, 6 and 10 were relatively the strongest decision rules, supported by two case studies. Rule 3 states that when gravity of the availability of financial capital is small the perceived international market access is perceived as neutral. Apparently companies with financial capital do not perceive international market as problematic. Rule 4 refers to reimbursement. If a company does not known the gravity of reimbursement, then a company perceives the degree of difficulty of market access as well as neutral. The perceived degree of difficulty may changes when the companies achieve more experience with the reimbursement requirements.

Furthermore rule 6 equally weak as the other abovementioned rules, indicates that if a company has orphan product, the gravity of the availability of financial capital is large and the gravity of the management team is small, then the degree of difficulty of international market access is perceived as problematic. It appears that this specially account for orphan products with a coverage of 14.3%. Decision rules number 10, suggests that if the gravity of the TPP requirements is large and the gravity of regulations is small then the perceived degree of difficulty of international market access is high.

The decision rules and the perceived degree of difficulty of international market access are shown in Table 10.

Table 10: List of decision rules and their strengths of RSDA

Conditions in rules	Rules, number of cases and coverage (%)
Perceived degree of difficulty of international market access: easy	
Management team	Rule 1: 1 (7.1%); gravity of management abilities is not known
Perceived degree of difficulty of international market access: neutral	
TPP - Reimbursement	Rule 2: 1 (7.1%); gravity of TPP requirements is low and gravity of reimbursement is low
Financial capital	Rule 3: 2 (14.3%); gravity of the availability of financial capital is small
Reimbursement	Rule 4: 2 (14.3%); gravity of reimbursement requirements is not know
Pricing – Reimbursement – Regulations	Rule 5: 1 (7.1%); gravity of appropriate pricing is low, gravity of reimbursement is high and gravity of regulations is low
Perceived degree of difficulty of international market access: problematic	
Product type – Financial capital – Management team	Rule 6: 2 (14.3%); orphan drug type, gravity of availability of financial capital large and the gravity of management team abilities is small
Management team – Regulations	Rule 7: 1 (7.1%); gravity of management team abilities is large and gravity of regulations is not considered yet
Reimbursement – Management team	Rule 8: 1 (7.1%); gravity of reimbursement is low and gravity of management team abilities is neutral
Perceived degree of difficulty of international market access: very problematic	
Financial capital	Rule 9: 1 (7.1%); gravity of availability of financial capital is neutral
TTP - Regulations	Rule 10: 2 (14.3%); gravity of TPP requirements is large and gravity of regulations is neutral
Management team	Rule 11: 1 (7.1%); gravity of management abilities is not known

No decision rules involve the size of the companies, the creation of awareness or risk sharing agreements which indicates a relative low power in the decision rules. These factors due have exploratory power of the decision variable but do not influence the determination of the perceived degree of difficulty of international market access. The size however would Furthermore, when gravity of abilities of the management team is not known a company can perceive market access as easy or as very problematic. These differentiating results are probably related to the lower management team experiences of the companies.

From these results trends can be described. It could be seen that to achieve a more clear view on the degree of difficulty of market access senior managers need to be aware and involved with management abilities and the reimbursement requirements which are the condition attributes with the highest frequency in the rules and have a strong power. In addition regulations and financial capital have a strong power to determine the perceived degree of difficulty of international market access.

Rough Set Data Analysis 2

To assess the strength of the different of absorptive capacity factors RSDA2 was performed. The condition attributes were again divided under two headings namely the *characteristic information* of the companies and the *market access information*. The characteristic information in this analysis included the size and the age. The market access information was bases upon the management team abilities. The decision attribute is again the perceived degree of difficulty of international market access.

The data representation is categorical for all the attributes except for age which is continuous. In this case the no three-class classification was adopted for the management abilities as this would decrease the quality of the classification and would have resulted in a less useful rough set analysis.

Table 11: Explanation of the factors for RSDA

Name	Explanation	Category
Characteristic information		
C1: Size	Number of employees/fte of the company	Categorical: 1 = 0-10 employees, 2= 11-50 employees, 3= 51 or more employees
C11: Age	Age of the company	Continous: between 1 and 16 years
Market access information		
C8: Management	Management abilities	Categorical: 1= very small gravity, 2= small gravity, 3= neutral gravity, 4= large gravity, 5 = very large gravity, 9= not available as these are not considered yet, 10= not available as the variable is not relevant, 11= not available as it is not known
D: Market access	Degree of difficulty of international market access	Categorical: 1=very problematic, 2= problematic, 3= neutral, 4= easy, 5= very easy

A similar information table as shown in Table 11 was created. The approximations and the frequencies of the attributes can be found in *Appendix: RSDA approximations, frequencies of attributes and the core attribute*.

In the interpretation of the rough set results the frequencies was looked at. The condition attributes with the highest frequencies were age and the management team abilities.

Also the coverage of each rule was used to interpret the data. The highest level of coverage in the analysis was 14.3% (2/12) but most did not exceed 7.1% (1/14).

Shaping factors of the perceived degree of difficulty of international market access

After the RSDA application 13 rules were which explain the different levels of perceived difficulty of international market access. The discussion no decision rules were excluded however in this discussion only the strongest decision rule will be discussed.

When the condition attributes in the decision rules are considered two attributes had a relatively strong power namely the age and the management team abilities, occurring 4 and 7 times. The frequencies of the condition attributes can be seen in *Appendix K: RSDA2 Results of the rough set analysis.*

Table 12: List of decision rules and their strengths of RSDA

Conditions in rules	Rules, number of cases and coverage (%)
Perceived degree of difficulty of international market access: easy	
Age	Rule 1: 1 (7.1%); age is 5
Management team	Rule 2: 1 (7.1%); gravity of management abilities is not known
Perceived degree of difficulty of international market access: neutral	
Size – management team	Rule 3: 2 (14.3%); size is small and gravity of the management team abilities is large
Age	Rule 4: 1 (7.1%); age is 13
Age – management team	Rule 5: 1 (7.1%); age is 3 and gravity of the management team abilities is very large
Perceived degree of difficulty of international market access: problematic	
Age	Rule 6: 1 (7.1%); age is 2
Age	Rule 7: 1 (7.1%); age is 9
Management team	Rule 8: 1 (7.1%); gravity of management team abilities is small
Age – management team	Rule 9: 1 (7.1%); age is 3 and gravity of management team abilities is large
Perceived degree of difficulty of international market access: very problematic	
Age	Rule 10: 1 (7.1%); age is 4
Age – management team	Rule 11: 1 (7.1%); age is 1 and gravity of management team abilities is very large
Age	Rule 12: 1 (7.1%); age is 16
Age – management team	Rule 13: 1 (7.1%); age is 3 and gravity of management team abilities is neutral

From the analysis it could be seen that rule 3 was relatively the strongest decision rules, supported by two case studies. Rule 3 states that when size is 11-50 employees and the gravity of the management team abilities is large the perceived international market access is perceived as neutral. Senior managers in medium sized companies who believe management team abilities have a very large gravity perceive the degree of difficulty of market access as well as neutral because these companies may be able to fill the lacking management abilities.
From these results it can be seen that the frequency of the variable size was once. The explanatory power of this conditional attribute included to analyze absorptive capacity is therefore low. In the first RSDA was found that size had no frequency within the rules and has no power in determining the perceived degree of difficulty of international market access.

So the age following from the decision rules has explanatory power to determine the perceived degree of difficulty of international market access within the variable absorptive capacity. However in practice it could be seen that the age does not play a role in the determination of the perceived degree of difficulty of international market access. Both young and old companies perceive degree of difficulty of international market access as very problematic. The age in practice, however, may not have a strong power because companies can license in products or can be a virtual company and outsource many activities.

From these results it can noted that companies with a age of three years and with a large gravity of management team abilities perceive the degree of difficulty of market access as neutral. However, a company with the age is 1 and gravity of management team abilities is very large perceives the degree of difficulty of market access as neutral very problematic. This could be attributed to the lower experience of the management team in the industry or due to the type of product of the company.

According to the results of the analysis in determining the perceived degree of difficulty of international market access all the absorptive capacity factors play a role. But the extent to which these play a role in the determination of perceived degree of difficulty of international market access differs.

7.4 Summary and conclusions

- From the database 51 small to medium size life science and health ventures were selected, with drugs development phases ranging from the discovery phase up to marketed products phase, had been selected for survey analysis and they have to have products that need to encounter clinical trials.
- Data is obtained from 14 respondents by means of a survey (including a shorted survey), in-depth interviews and triangulation. From the data of the respondents it appeared:

  Characteristic results
  - The senior managers did not stay for many years with the same company.
  - M_{size} = 1.64 thus the average sample size was between small (11-50) and medium sized (51 and more). The M_{age} = 6.71 year, SD_{age} =5.090 and the age of the companies ranged from one to 16 years.
  - Most of the companies had a turnover below the 100.000 and did not have revenues from services or cash cows.
  - As well the companies in the sample varied in the development phase and approximately 30% of these companies is not involved with clinical trials.
  - The ventures differ in product type too, 5 out of 14 companies is focused on the development of orphan drugs.
  - The indications of the product varied and some of these are oncology, dyslipidemia and depression.

- 50 percent of the companies received funding from VC's and some others from an IPO when the companies were in a later stage of product development.
- Management teams differed from one management member to eleven MT members and sometimes managers worked part-time for a company. Among these MTs the business experience and international experience varied highly. Some companies as well have specialists in the management team with operating and supply chain experiences.

Market access results

- The results on the market access showed that 64.3 percent of the company believe market access to be problematic or very problematic. The respondents attributed the market access challenge mainly to availability of financial funding convincing data and narratives, the innovativeness to potential (big) partner and regulatory authorities. Political barriers and non-harmonized regulations are as well perceived as problems.
- Companies' respondents ranked potential market access barriers and the degree of difficulty of international market access. From this data the causality of barriers and the perceived degree of international market access was derived. To find underlying trends with a small sample, a level of measurement of the data and fuzzy data RSDA was applied.

RSDA1

- The highest coverage is 14.3% for four rules, the other rules have a coverage of 7.1%. All the decision rules show weak coverages.
- The frequencies show that all condition attributes have exploratory power. The attributes with the strongest explanatory power are the TPP requirements, management team abilities and the risk sharing agreements.
- The condition attributes with the highest frequencies in the rules are management team abilities and reimbursement requirements
- Size, creating awareness, risk sharing agreements did not appear in the decision rules did not appear in the decision rules, however they do have power to explain the decision variable but do not influence the determination of the decision variable.

RSDA2

- The highest coverage is 14.3% for four rules, the other rules have a coverage of 7.1%.
- The frequencies show that only the condition attributes age and management team abilities explain however exploratory power. The condition attributes with the highest frequencies in the rules are again age and management team abilities.
- In practice the age however does not determine the perceived degree of difficulty of international market access.

The frequencies of the condition attributes C2-C11 explain the perceived degree of difficulty of international market access. Hence, these factors have to be included in the decision-support tool. The size condition attribute does not have strong explanatory power of the decision attribute, though it needs to be taken into account in the decision-support tool because virtual companies are more concerned with financial capital or making agreements.

8. DECISION-SUPPORT TOOL DESIGN

The decision-support tool, the checklist, was designed on the basis of the results from a literature review, in-depth interviews and triangulation. In this chapter you will be able to follow the steps in the development of the checklist for managers prior to market access.

8.1 Design of the checklist

Items in the checklist

The results of the RSDA were interpreted and all the condition attributes contributed to the explanation of the perceived difficulty of international market access and therefore these should include in the tool. Besides, the differentiating factors identified in RSDA, other factors such as 'comparators' and 'effective negotiation' had to be included in the tool because these also play a role for small ventures in the pharmaceutical industry (section *Results*). In addition, other characteristics are important in pharmaceutical companies which should be added to the checklist to obtain a clear overview of all the elements to provide proper guidance to managers (section *Small technical and pharmaceutical ventures*).

A distinction in the checklist was made for orphan drug companies and gene therapy companies. These companies have to be aware specifically of some factors. Furthermore companies need to consider different business model strategies that can be applied before product launch.

Development and drafting of the checklist

For the development of the knowledge-driven decision-support tool, criteria were taken into account which can be seen in Figure 9. This checklist supports the design of the checklist and helps to assess the final outcome.

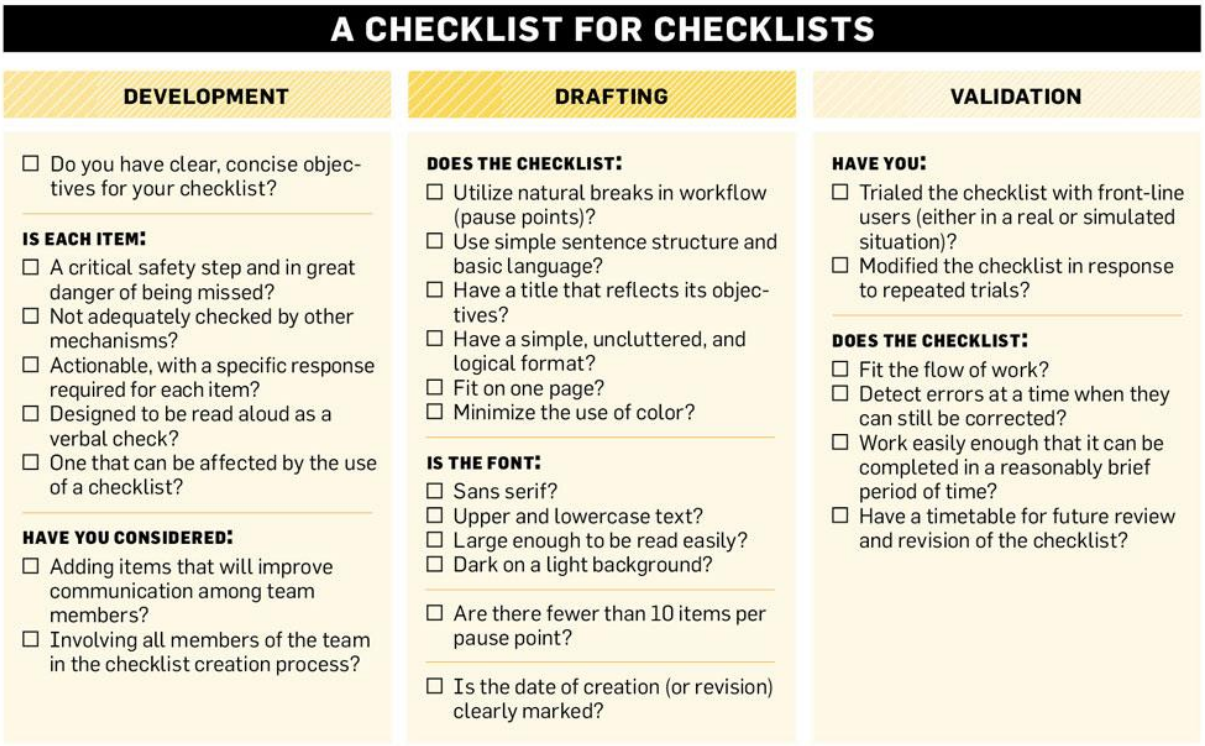


Figure 9: Checklist for checklists (The Build Network Staff, 2013)

The designed checklist has clear concise objectives. For each variable it was verified whether it is a critical variable and dangerous if being missed. In this case dangerous does not fit this study, as this

would be more applicable to practical procedures for e.g. nurses but for this checklist it is important that critical factors are not missed. The factors were actionable and not overlapping. In addition the checklist was controlled to be read out loud as a verbal check.

This checklist did not add factors to improve communication among team members, however it does stimulate management team members to organize a discussion in which these factors are addressed.

The checklist does have natural break points in the workflow, it uses simple sentences and basic pharmaceutical industry language. The title reflects the objectives and it has a simple format. Unfortunately it does not fit on one page. However, it is well structured on seven pages with first an forward, followed up by generic factors and specific factors for specific companies. The collars are minimized. An appendix with more information is added to the tool.

The font is not sans serif, there is upper and lowercase text. The text is large enough to read and dark text is on a light background. There are fewer than 10 point per pause point and the date/month of creation is present.

The validation will be described in the next section.

In section *4.2 Requirements of the decision-support tool the checklist*, other requirement were mentioned and the need to be assessed.

Table 13: Checklist requirements

Requirements	**Comments**
Created by people who have an understanding of the situation	Senior managers and experts were interviewed and the checklist was validated against expert views
Brief, to the point and easy to read (Gawande 116)	This was considered during the design
Wording has to be simple (Gawande 123)	This was taken into account during the design
Precise and easy to use (Gawande 120)	This was taken into account during the design
It should not try to spell out everything; a checklist cannot perform a 'surgical operation'. It is a list of reminders of the most critical and important elements even one's highly skilled professionals could miss (Gawande 120)	Not too many guidelines for experts
it should be practical otherwise it will be unused (Gawande 120)	Considered during the design phase
Exhaustive including all the necessary factors	Considered during the design phase
Reasonably brief period of time to complete the checklist	Considered during the design phase
Criteria	**Comments**
Does the checklist recognizes the market access strategy the heterogeneity in the market (different countries?)	Due to the fact that reimbursement differs in each market such as the patient diagnostics and screening.
Does the list anticipate at changes in the market?	In the introduction of the tool describes that the pharmaceutical industry is constantly evolving and dynamic and that new tools are being created and the tool is as well dynamic.
Does the checklist take into consideration the strengths and weaknesses of the product relative to appropriate comparators?	The comparators and the advantages of the company's product are taken up by the checklist.
Does the checklist anticipate on the management abilities?	Several questions are related to the management abilities.

8.2 Validation of the checklist

After the development the checklist had to be validated against expert interviews or front line users. The checklist was modified in response to the performed discussions. The first validation was performed with an experienced person in the industry. The expert has finished a Ph.D. and an MD and has a background in medical sciences. The expert's experiences include: managing a laboratory, co-founder of several companies, peer reviewer of more than 500 scientific papers, board member of several companies internationally and involvement with financial and commercial advice on new products. The second validation was performed with a senior manager of a small venture in the Netherlands who has over twenty years of experience in the industry, to take into consideration a senior manager's perspective on the decision-support tool.

In this validation discussions the different factors in the checklist were discussed, the utility and the desired timeline of the tool.

Potential factors to add to the checklist

- The company's product type can also be divided in medical devices and drug development products. For these former products the market in Europe is at the leading edge of these type of products which influence the launching sequence of medical devices products. In this case the study focuses mainly on drug development companies which should be highlighted in the title.
- Manufacturing deserves more attention as many entrepreneurs often do not consider the manufacturing and the economic feasibility. This should be added to the tool.
- Intellectual property needs to be considered by companies. Often many activities are not well protected and companies need to be careful.
- Members of the board should not be afraid to see their share in the company declining. Because as a shareholder would you prefer 50% of company that has low value, or 5% of a company that is has a value of 500 million?

Additional information on current factors

- The competitive landscape should be included because a company should consider whether or not to enter this field when a similar product is developed in other country and is already further in the development.
- KOLs are highly important prior to market access. Companies acquire a medical or scientific manager with a large scientific track-record to have access to the KOLs.
- Successful small ventures desire a professional management team with business experience. The management team abilities have to be strong otherwise financial capital cannot be attracted. Managers with international experience are desired. However, this necessity relates to the phase of the company.
- Creation of awareness depends on the product type. For orphan disease companies it is important to know the demands of their target population and opinion of their KOLs.
- Pricing of the product is concerned with the return of capital, the time and many other factors such appropriate pricing per country, which are the target areas. During the pricing phase companies often consider the marketing cost and the marketing ramp of the sales.
- Patient infrastructure highly depends on the indication of the product and companies could be aware of the difficulty finding the right patients during the clinical trials.
- HTAs may be highly difficult because survival benefit data has to be generated to assess the total cost. During the clinical trials KOLs and patient discussions could help to determine a valid endpoint which is difficult to determine for orphan disease products.
- Business model strategies should be considered by companies prior to product launch. The type of product such as a small molecule, synthetic peptide or a monoclonal antibody

determine whether a dedicated small team of employees is enough to develop and to bring the product further in the development. These virtual companies can outsources many activities but have to control, manage and integrate the outcomes of the various activities (e.g. clinical development, dealing with the regulatory authorities, manufacturing).

- Companies can consider in a later phase to go for exit opportunities. These include the options, licensing out or selling to a large pharma company, merging with a smaller biotech/pharma company or make an IPO. However a company cannot independently decide on these options because a company is dependent on the current situation and for example the best time for an IPO. When the company wants to license out the product or wants to be acquired it needs to consider the requirements and the controls for chemistry and manufacturing which are accepted by large companies (Specs).

Utility of the checklist and the timeline

The checklist was considered to be useful to increase business knowledge in addition to scientific knowledge. Ambition of managers to reach its goals is good but sometimes managers are ignorant and naïve. The tool definitely increases awareness and managers can reflect critically on their current strategy and activities. The tool can be used by managers to develop a business plan or a value proposition. The checklist is product dependent and for each new product the checklist has to be reconsidered. Sometimes it may be too early for a company to address the different factors mentioned, argued the second expert. However, the first expert argued that it provided entrepreneurs to take a bird eye view and to obtain a long-term perspective. Managers should be aware of the overall picture and can then zoom in at the factors that have priority in the specific phase of the company.

8.3 The checklist

After validation the checklist was adapted and the revised checklist can be found below in figure 11. The tool includes an appendix as well which can be acquired upon request.

August 2014

Reviewing your international market access chances

Completing your company's strategy, by seeing opportunities for successful market access at a glance.

This checklist allows pharmaceutical entrepreneurs to:

- Address the key factors of international product launch in the market that need to be dealt with to optimize opportunities and minimize hurdles
- Identify and comprehend stakeholders in international market access

In the appendix additional information on key factors, stakeholders and business models is provided.

Due to the fact that the pharmaceutical industry is constantly evolving and dynamic and new tools being created this DST is by nature as well dynamic. Therefore this tool can be seen as 'work in progress' as new ideas and experiences become available over the time.

Generic factors of interest

Have you considered: *Product characteristics*

- ✱ ❑ the TPP requirements?
  - acceptable evidence of safety and efficacy?
  - the prevalence and severity of any side effects?
  - relative convenience an ease of administration?
- ❑ The number and clinical profile of comparators?
  - advantages over alternative treatment methods?
- ✱ ❑ The reimbursement requirements?*
- ❑ The submission for designations?
- ❑ Up scaling of the product?
  - in-house or not?
  - by a potential partner?
- ❑ Proper Intellectual Property (IP) protection?

*** Note: Dependent and independent timelines have to be considered. The timelines of several items can be influenced by the company. The reimbursement timeline for instance cannot be influenced. Therefore you should not promise launch dates of the product internally and/or externally.**

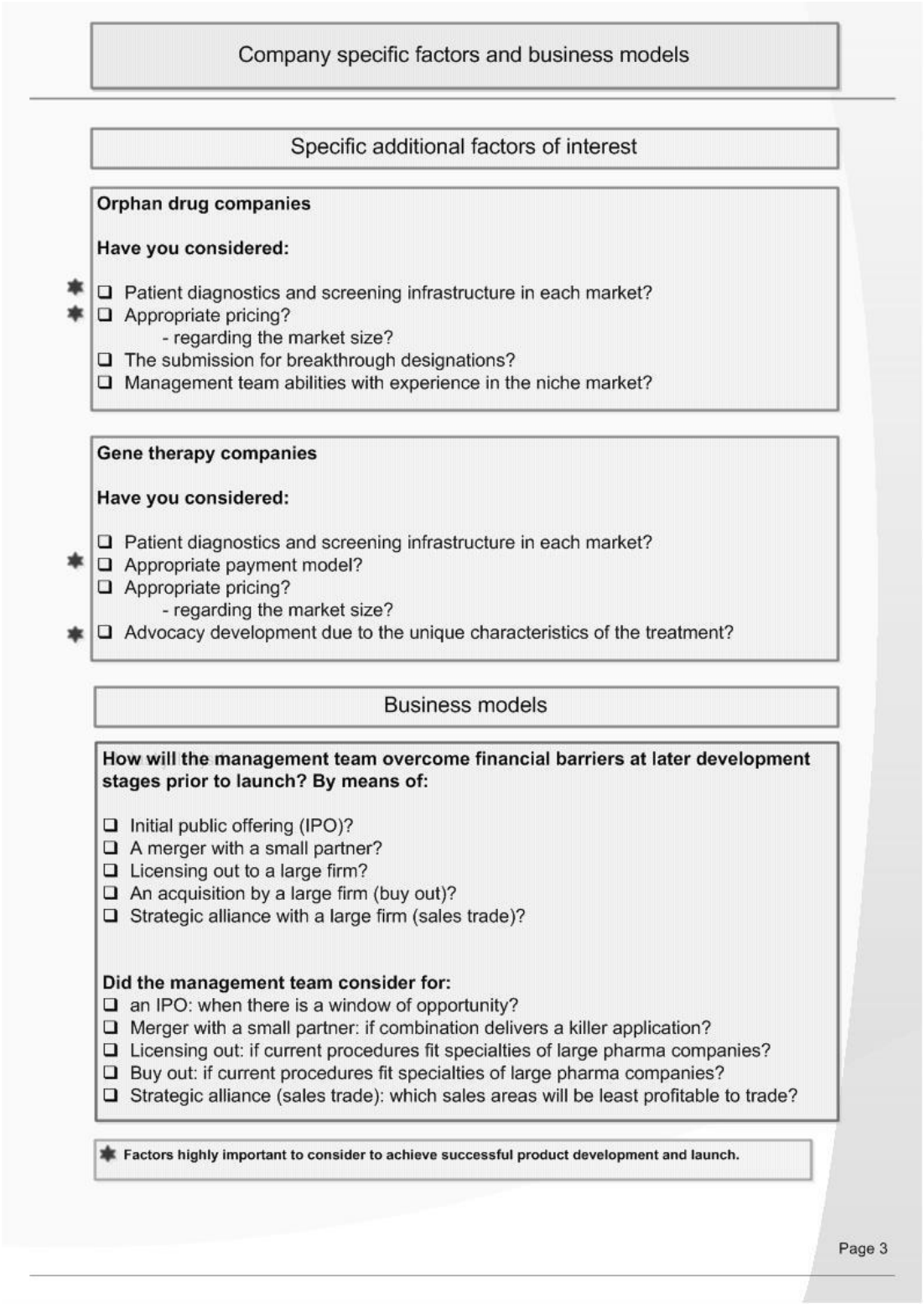
Is your company: *Company characteristics*

- ❑ Represented by lobbying groups?
- ❑ Involved with the awareness creation?
  - patient societies
  - advocacy development
- ✱ ❑ Informed about the opportunities of financial capital?
- ❑ Informed about the opportunities of financial available incentives?
- ✱ ❑ In possession of a strong management team?
  - sufficient knowledge of key expertise (therapeutic field)?
  - sufficient capability to access scientific and business networks?
- ❑ Owner of a focused product portfolio?
- ✱ ❑ Concerned with commercial outsource/in-house opportunities?
  - commercial activities (launching and penetration)?
  - specifications of large companies?

Have you addressed: *Sector characteristics*

- ❑ International regulations concerning your product?
- ❑ The influence of payers on reimbursement and pricing?
- ✱ ❑ The role of Key Opinion Leaders related to reimbursement?
- ❑ The general requirements for (non-harmonized) Health Technology Assessments (HTA)?

✱ **Factors highly important to consider to achieve successful product development and launch.**



8.4 Summary and conclusions

The decision-support tool had been designed and validated against two expert views. The experts stated that the checklist could support managers in the design of their business plans. It should provide an overview of important factors which can guide managers, from the discovery phase up to a marketed product, but it should still offer starting companies the freedom to focus on the first steps. The checklist would be helpful for managers to gain insight into the critical factors that have to be considered during the product development and it creates awareness among the managers about the desired endpoint, the market.

9. DISCUSSION

In this chapter the differences in results of the companies characteristics and the companies respondent' market access rankings will be discussed. In addition the use and the RSDA results and the decision-support tool will be elaborated on.

Companies characteristics

- It is important to remark on the age of the studied companies. Three products from these companies originated from earlier days. The first product was outlicensed by a large company to a smaller company after several development phases. The second product was developed in a company which was later transformed into another company. The third product was sold by company (A) and then bought back after company's (B) rejection of the development. In this research, however, the ages of the companies did not provide explanatory power to justify the perceived degree of difficulty of acquiring international market access and therefore this factor will not influence the interpretation of the data.
- During the interviews, discussions about the turnover quantification of companies arose. Only one company in the sample obtains revenues from a marketed product. The other companies acquire income from collaborations or strategic alliances. The latter source of income can be defined as turnover, however, since these are not revenues from sold products in the market, comparison based on the turnover was not possible.
- After the interviews it also appeared that it was difficult to define the product type. One respondent mentioned that clinical studies strategies could be altered. When financial capital would not become available or when no partner could be found in the future, the drug would be altered into a drug with an orphan indication. A product can be submitted for an orphan indication as long as the rational is grounded. In this study the current indication of the product orphan/non-orphan has been taken into account.

  Other product type characteristics, platform technology for example, have not been considered during the analysis, things which may be interesting to consider in future research.

  One company in the sample will not provide products to be prescribed by physicians but those that are to be used by physicians. This has implications for the quantifications of the factors such as creating awareness among patients societies.
- The main indication of the products could alter during the development process. One respondent mentioned that the indication of the product may be altered due to KOLs suggestions. The current main product indications are taken into account in this study.
- The information gathered on cash cows were focused on revenues from market products or from delivered services. In this studycash cow revenues of a company's marketing agreement also included in the cash cow group. By taking different sources of cash cows into account, this can influence then the number of companies having cash cows.
- Concerning the management teams it is noteworthy that some comprehended managers who work part-time for the company. From a validating expert discussion, it appeared, however, that if companies trully aim to develop a product from the discovery phase until marketed products, CEOs in particular have to be committed and fully dedicated to the firm.

Market access

- The results on the market access showed that 64.3 percent of the companies considers market access to be problematic or very problematic. Naturally, different perspectives exist on the definition of market access. Market access can be seen as the access of the product to the market involving regulatory approval, reimbursement and if necessary HTA procedures. Market access can also be seen as the process after regulatory review when the product is approved and the scale of the product in the market has consequently to be expanded by

increasing market acceptance and stimulating market penetration. In this study, the first perspective on market access is used as the definition of market access.

- In this research the gravity of the factor direct comparators needed to be ranked as well. Some companies, however, do not have any comparators because they are pioneers in their market, as is often the case for orphan drug companies. For these pioneers, benchmarking is not possible and clarifies differences in rankings.
- Lobbying for new business models for a new payment infrastructure is applicable to companies producing e.g. gene therapy products. For such companies, reimbursement and HTAs are challenging due to the newness of the product. In this study, a gene therapy company is included in the sample which explains differences in rankings of factors' gravity to market access.
- Appropriate pricing depends on the product of the company. Some companies obtain a competitive advantage by producing 'cheaper' drugs and for these companies, benchmarking is possible. Orphan drug companies or gene therapy companies are confronted with difficulties of pricing of their medical products because no reference exists. These types of companies perceived higher gravity of the variable appropriate pricing. Due to specific factors that play a role for these companies, these two specific company types achieved specific attention in the tool.
- Creating awareness differs per product type and per product indication. For companies with orphan disease products and a widespread small market size, creating awareness of the gravity of the variable was not ranked high. Their patients are too widespread and not often joined in patient organizations. The differentiation in rankings could be explained by the development of the products' niche markets.
- Financial capital is a barrier for most companies, except for those with recently obtained investments, explaining the differentiation in the ratings of the gravity of the variable. Similar results were found for the variable lack of financial incentives. These incentives, however, are more applicable to early stage of development companies and are less useful in execution of a clinical study. According to the validation interview it is recommended to change the incentive culture towards the Canadian structure where companies do not pay clinical trial taxes.
- The results of the lack of risk-sharing agreements need to discussed. These risk-sharing agreements can be achieved for R&D or for marketing. A marketing agreement was the definition, but survey respondents may have interpreted the variable differently. As such, the results are less reliable. The lack of marketing agreements received a large gravity to market access for the virtual companies in this study since these often strive for or demand an exit after phase III. Differences in ranking can be explained by differences in business models of the companies.
- Effective negotiation was also argued to be very important for companies. Some companies ranked this with a low gravity to market access due to the presence of a good management team. Linked to this are the management team abilities, whose gravity to market access differed per company depending on the team.
- Overly strict national regulation received a large gravity to market access by companies with a highly unique product and one triggering ethical discussions. Different ranking by respondents can be justified by the specific products. One company emphasized that the barrier for pharmaceutical companies are the non-harmonized regulations.
- In addition, most companies in the sample place a high gravity to KOLs but they have different rational. One company involves their KOLs in the preclinical phase to get strategic guidance, while others approach the KOLs later in the development.
- Some companies are not familiar with the HTA, and this lack of knowledge recommends guidance to provide managers with awareness prior to market access.

It was remarkable that some managers did not provide or rank potential barriers. In this study, these missing values had been valued, assessed and obtained codings along the lines of not available as these are not considered yet, not available as the variable is not relevant, not available as it is not known. It is important to take these absent answers into account as they can have implications for this study. A decision-support tool could support managers of discovery phase companies to become aware of the critical factors for small ventures regarding market access and provide a birds-eye view on the development of a product.

Rough Set Data Analysis

- From the RSDA, it can be seen that the coverages of the decision rules in the two analyses are relatively low and maximum 14.3 percent. More case studies should be included to support the observed trends related to the perceived degree of difficulty of international market access.
- The frequencies of the condition attributes TPP requirements, management team abilities and risk sharing agreements appeared to be the highest. In addition the frequencies of the product type, creating awareness and regulations showed a higher frequency than financial capital. Although financial capital was perceived by most companies as a large barrier, it has relatively a low explanatory power concerning the degree of difficulty of international market access. The condition attributes with the highest frequencies in the decision rules are management team abilities and reimbursement requirements, both of which had a relatively strong power in the determination of the degree of difficulty of international market access strategies. Size, creating awareness and risk sharing agreements did not appear in the decision rules indicating that these factors do not influence perceived degree of difficulty of international market access strategies. In practice, however, sharing agreements do influence perceived degree of difficulty of international market access. The second RSDA, solely looking into the absorptive capacity factors, showed frequencies for the condition attributes age and management team abilities. Both tend to influence the perceived difficulty of international market access and these had also the highest frequencies in the decision rules. From the interviews, however, it could be derived that age did not play a role in the perceived degree of difficulty of international market access due to e.g. inlicensing and transformations of companies into new companies. The analysis with continuous number for the age was weak. Categorization has been tried but the quality derived below one and could therefore not be used to analyze the data.
- From the RSDA, it is interesting to note that managers who perceive the gravity of reimbursement requirements as large, believe international market access to be problematic. Managers who perceive the gravity of reimbursement requirements as low or those who do not know the gravity, believe international market access is easy. This suggests that managers who know more about international market access factors realize market access to be more problematic. This suggestion supports providing guidance to small ventures on international market access concerning earlier hurdles and challenges.
- Furthermore, from the results, it could be seen that primarily companies with professional, experienced management teams (low gravity of market access for management team abilities) believe international market access to be difficult. Guidance concerning international market access to small ventures could contribute to the awareness of managers.

Decision-support tool

Many factors attained different ratings, and explanations for these differences were provided and discussed. By using the obtained data and the observed trends from the RSDA, a decision-support tool was developed and validated. The tool, which is highly specific per product, was assumed to be valuable for managers to design a proper value proposition when the companies want to attract investments or partners or to create awareness among today's entrepreneurs.

10. CONCLUSIONS AND IMPLICATIONS

In this study the aim was to explore the critical success factors for market access, as perceived by companies, and to design a decision-support tool to provide guidance to managers prior to market access. By means of a literature review, online survey and in-depth interviews with companies and experts barriers of international market access had been identified and explored.

On the basis of a literature study, current challenges and trends were assessed to identify potential barriers of international market access for small pharmaceutical companies. Today, pharmaceutical companies face many challenges and these include different requirements in diverse markets for health technology approval and reimbursement, augmented reliance on Health Technology Assessments (HTAs) and the specificity of the assessments per country, appropriate pricing, value drivers of new market stakeholders and consolidation. Several of these challenges and associated factors were measured in this study to assess the gravity of the potential barriers to market access.

Alongside, these challenges posing barriers, small pharmaceutical ventures are concerned with: the lack of knowledge or experience, high risks of product failure, enough skilled scientists and business persons, effective negotiation skills, less developed network of the company and availability of financial capital for the expensive development of drugs. Next to these factors, factors related to the product suggested barriers to international market access play and important role, examples being TPP requirements, comparators, appropriate pricing and reimbursement. In addition sector or market factors were supposed to form barriers like (inter)national regulations, payers and HTAs. From this research it can be concluded that several of the potential barriers were confirmed to be barriers and had a ranging gravity to the degree of diffulty to international market access.

It this study, it was determined that 64.3 percent of the respondents perceived market access as (very) problematic, something which contributes to aim of the study. The selected sample for the in-depth interviews were selected on the basis of differentiation factors.

The selected sample in this research (N=14, M_{size} = 1.64, M_{age} = 6.71 year, SD_{age} =5.090) included companies with various product indications such as CNS, Multiple sclerosis, oncology indications, depression, dyslipidemia and health aging. Among these products, orphan disease products and a gene therapy product were present. The product type influenced the rankings of the gravity of potential market access barriers by the respondents.

The respondents in the sample mainly attributed the market access challenge to availability of financial funding, convincing data and narratives and the innovativeness. Political barriers and non-harmonized regulations are also perceived as barriers.

From the results of the study, it can be concluded that the TPP requirements, management team abilities, risk sharing agreements tend to highly influence the perceived degree of difficulty of international market access. Other factors such as size of the company, product type, pricing, reimbursement, creating awareness, financial capital and regulations also influence the perceived degree of difficulty of international market access, however, these have a lower explanatory power. In addition comparators, effective negotiation, payers and HTAs play a role.

Furthermore, the coverage of decision rules as the results of the rough set analysis tended to be weak with a highest coverage of 14.3 percent. The observed trends may be stronger but more case studies are required. Management team abilities and reimbursement requirements tend to be two factors with relatively strong power whereas these had the highest frequencies in the decision rules. The company's size, creating awareness, risk sharing agreements tended not to play a role in the trends and the determination of the degree of difficulty of international market access. More research is needed with a clearly defined 'risk-sharing agreements' variable as this variable may have a stronger role in trends.

In the part of the study on absorptive capacity, age and management team abilities had a relative strong einfluence on perceived difficulty of international market access and a relative strong power regarding the trends. The power of the age factor tended to be smaller in practice. Remarkably, the age and the size, often control factors for absorptive capacity, tend not to play roles in degrees of

difficulty of international market access due to respectively the opptunity of inlicensing of products and a virtual business model.

Beside the aim to explore the critical factors of market accesss the goal of this study was to design a decision-support tool. All factors related to international market access were included in the tool, the most frequenctly ones in the rules being highlighted by stars.

The decision-support tools help decision makers lacking information, experience or do those with not enough knowledge regarding the decision that has to be made. To guide managers with decisions related to long-term objectives and to help them to deal with incomplete information a decision-support tool was designed. Often, full rational decisions are not possible because of the lack of information. This could lead to heuristics, cognitive short-cuts, which could create biases in choices. To avoid this, the decision tool will help managers avoid errors of ignorance and errors of ineptitude. In this study, a knowledge-driven tool, was designed which fitting specific requirements of an effective and practical checklist. This checklist does take into account the dynamics of the industry and the heterogeneity of the countries. In this study, the do-confirm checklist is adopted rather than the read-do list - to give managers greater flexibility in performing their tasks.

The decision-support tool will support managers who lack information or experience to design a business plan or - in a later stage –market access for a new product. To critically assess the different factors, managers can use the checklist on their own or with the management team on a given day.

The checklist contains general factors for small pharmaceutical ventures, specific factors of interest for orphan and for gene therapy companies and a section related to business models. The checklist had to meet several requirement such that it had to recognize heterogeneity in the market and whether the list anticipated on changes in the market.

The checklist is helpful for managers to consider market access during the product development and create awareness among the managers about the desired end point - the market. This checklist stimulates innovative companies to focus not only on the scientific process. But on the market perspectives which could also lead to more and faster successful commercialization of products.

The scientific and managerial implications will be described in more detail in the next sections as will the implications for policy makers be touched upon.

Scientific implications

This thesis study provides better insight in market access factors and barriers of the pharmaceutical industry and has implications for managers in the industry, for policy makers and for the scientific community. Market access barriers have been obtained from the literature on market access trends and challenges.

Next to the market access potential barriers derived from the literature, the different factors of absorptive capacity and their influence on the perceived degree of international market access were assessed. In this study, the role of absorptive capacity in a marketing setting in the pharmaceutical industry has been analyzed. Most studies related to absorptive capacity in the pharmaceutical industry are related to R&D contexts, such as the study by Nicho US-Nixon (1993) that expanded on the findings of Pennings and Harianto. She looked into the role of absorptive capacity in pharmaceutical firms' responses to technological discontinuity created by the emergence of biotechnology. The absorptive capacity was measured by Nixon and her results showed that companies with higher levels of absorptive capacity invest more in their own R&D, as well as made use of alliances and had more in-house expertise. In this study, however, the causality between absorptive capacity and market access is assessed. It could be seen that companies with a low gravity of management team abilities still perceived market access as (very) problematic. In addition the age does not play a role in the determination of the perceived difficulty of international market access due, for example, to inlicensing of a product. The results show that a higher level of absorptive capacity (higher age, larger company, experienced management team) does not imply a lower degree of difficulty of market access.

Although more research is needed, this study adds value to the role of absorptive capacity in a marketing context. Lane (2006) mentioned that more studies should also focus on the role of absorptive capacity, the acquisition, assimilation, and commercial application on other types of business-related knowledge such as marketing expertise on which this study focuses (Lane et al., 2001). This study can contribute to this goal.

The research also provided information on the difference in the perceived views of the senior managers between the pharmaceutical companies. Market access can be perceived as the access of the product to the market involving regulatory approval, reimbursement and if necessary HTA procedures. Market access can otherwise be perceived as a process after a regulatory review when the product is approved, consequently expanding the scale of the product in the market by increasing market acceptance and stimulating market penetration. It appeared that market access may be difficult to address because of the ambiguity and diversity of definitions, components, antecedents and outcomes.

Additionally, thise research proposed a conceptual model. This model strives to explain the factors influencing the perceived degree of difficulty of international market access. The model is specific for the industry due to the variables of reimbursement, patients influence and HTA. The model is concerned with a regulated market which makes generalization of the model to other industries not possible.

The model was concise and the product, firm or sector factors could not be removed or elimated because the model dependent on the product type, and for each product different factors gain more attention than others.

Managerial implications

Achieving successful product commercialization became more crucial as R&D expenditure continued to rise over the past decade. Managers are confronted with a transformation in the industry to focus more on what the patient desires, to increase comprehension on the value drivers of new market stakeholders and to strive for treatments for health improvement. Companies adapt their commercial models to the current challenges and trends to obtain competitive advantages. To create innovative products that reach the market, managers ought to have scientific and business knowledge. Managers may lack knowledge or experience regarding market access, something that could be supported by a designed decision-support tool.

Managers with experience in this industry are scarce and well payed; this tool increases the amount of personnel that has scientific and business knowledge.

Managers who are aware of the missing experience or knowledge must acknowledge this and must look, in these cases, for external parties to aid them. This tool gives an overview of barriers and alleviates the need to hire an external party. A company has to realize that it lacks expertise or knowledge and consequently acquire people to fill these gaps.

Managers are forced to consider long term decisions as well, such as financial solutions for a phase study III. This makes managers aware of the opportunities and broadens their focus which strengthens the managers strategic decisions. Managers are required to think out of their comfort zone. Managers who considered an exit opportunity, for example, might now take this strategy into consideration. The tool enforces a company's position in strategic discussion with venture capitalists, other small potential partners and large pharmaceutical companies interested in collaboration.

The tool creates awareness among managers in companies with a unique product that requires the development of new business models and a new payment structure. In such a case, lobbying demands a different approach than normally, as many companies join a branche organization. In these cases the management team has to consider whether to lobby by themselves or to try to collaborate with a partner company which has experienced lobbyists and the proper network channels to achieve the goal of revised business models.

Besides managerial implications the study also has implications for policy makers. From this study it can be concluded that small companies hunger for financial capital but the current possibilities of

financial support are not sufficient enough. These small companies may be longing to political changes and new ways of financial aid. In Canada, for example, no taxes are paid for clinical studies which could highly stimulate small ventures to execute clinical trials.

In addition, and especially today, with the number of small ventures in the Netherlands rising this tool could add value. This decision-support tool provides guidance for small pharmaceutical ventures and can strongly support the goals of the Dutch government to excel the Life Sciences and Health sector by 2025. Additionally, the tool can contribute to the policy of grants and funds. Some companies attract money and investments while the feasibility of upscaling of product is not yet considered. This upscaling could be impossible or too expensive and early stage consideration of this feasibility could lead to different allocation of financial incentives by the Dutch government. The Life Science and Health sector should stimulate managerial use of this tool by means of distribution to branche organizations.

11. REFLECTION ON METHODOLOGY AND DATA SOURCES

In conducting an online survey in combination with in-depth interviews, it is appropriate to combine quantitative and qualtitative research. The study design was appropriate to explore critical success factors, to standardize scores and to quantify outcomes and to find trends by a systematic analysis.

Once concern that arises with in-depth interviews with specific cases (case study research) is that research often lacks rigorness. Rigorness is connoted by carefulness, sruptulouness and the degree of exactitude in the research investigations. This analysis, consisting of small sample, low levels of measurement of data (i.e. categorical) and the 'fuzzy' character of the data RSDA fit the research. For further research, it would be interesting to do a solid statistical investigation.

Another issue which may be considered to undermine the rigorness of the research concers manner of framing and addressing the questions during the interviews. Certain biases or incorrectness could have been to the responses. This may have been the case in the in-depth interviews with respondents of companies, were it not that the researcher had support from a highly experienced interviewer who aided in avoiding biases in the responses of the respondents. Reflexivity, through which in the interviewee expresses what the interviewer wants to hear was controlled with the help of the experienced interviewer

In addition, for case study research, it can be argued that the respondents in the organization could not or did not verbalize influences on market access during the interviews and therefore some influences have been overlooked. The respondents, however, were very open since the research was not focused on personal but on company perspective. Answers were treated anonymously, giving respondents the freedom to speak more freely. The interviews were recorded due to the broad information in the responses and the inexperience of the researcher. This could have led to biases in the responses, but due to anonymity, this would not influence the results.

The basis of generalization for case studies is little because the focus of the research is on generalizing theoretical propositions, just like experiments. The group of companies for the survey was selected by from a large database and consisted of 51 companies. The selection was based on factors such as phase of the main product and whether the company is involved in clinical study product. At times information obtained from the worldwideweb was not up to date , and could have influenced the outcomes of the selection of the sample. In general, however, it could be determined whether or not the company was intended to go through a clinical development. The respondents of the survey all held senior management positions which made comparisons between companies more reliable. The same also holds true for the respondents in the in-depth interviews. To overcome the limited data set acquired from the quantitative online survey which led to the results of fourteen companies for the rough set analysuis, in-depth interviews were performed.

The selection of the eighteen companies for in-depth interviews, was based on identified differentiating factors such as age, size, funding type and product type. This sampling focused on validating and external validity. By taking companies with diverse characteristics into account, the research results of the explanatory power of the variables and the trends are generalizable to those of other small pharmaceutical ventures. The results cannot be expanded to other small pharmaceutical ventures without clinical trials as the results of potential barriers to market access will higly differ, and so additional research will be necessary to do so.

It has to be stated also that case study research takes a long time and too much detailed and broad information may be acquired. The case studies took a long time and the interviews were difficult to plan too due to holiday seasons and the level of the respondents that needed to participate. Only senior managers were included in the study and to acquire an interview on their outcomes, patience was warranted. Often, senior managers are willing to speak when the company goes through a successful period, and likewise not open for an interview in difficult times. If all 51 companies could be included in the results the conclusions may be influenced. Having said that, even for 'florishing companies' market access was perceived as very problematic and so the inclusion of these companies would not alter these results. To find indications for the missing questions, annual reports were looked into, however, it would be best to approach the companies to collect any lacking information.

A good deal information was gathered. This led to the difficulty of clearly defining the scope. Network positions or collaborations agreements for instance are interesting for further research but were not included in detail in this research. The specific details of the factors such as reimbursement are discussed in literature due to their complexity, but details were not taken into account in this research.

On the other hand, the in-depth interviews made the data collection adaptive and flexible and this created opportunities which were is especially helpful in explorative studies. A factor such as up scaling for the product, something which could be a barrier, would otherwise not have been taken into account.

12. RECOMMENDATIONS FOR FUTURE RESEARCH

The suggestions for further research on influence and barriers of international market access for small pharmaceutical ventures would focus on several factors that were neglected in this study.

For instance, in the research, the products could be categorized in platform technology and non-platform technologies and gene-therapy and non-gene therapy. Analyses can be done by including these condition attributes in a RSDA.

Several other factors were assessed in the research but could be used in the RSDA due to a limited grid. Factors that could be taken into account are the lack of risk sharing agreements, payers influence and key opinion leaders' influence.

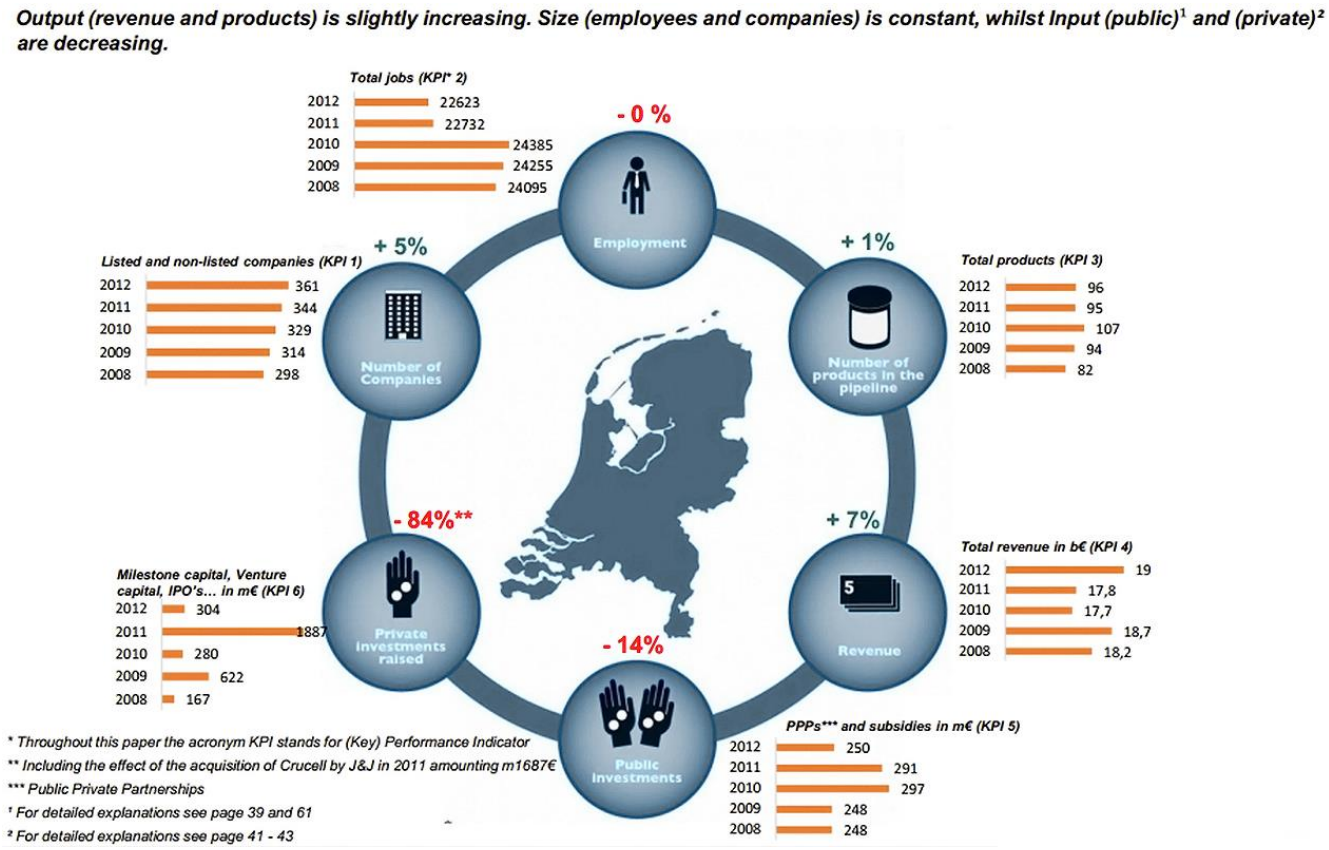
Furthermore, more research has to be done to collect proper data about the potential barrier of advocacy development, upscaling of the product, non-harmonized regulations and physicians influence.

Looking into the collaboration agreements of the companies and the network of partners will be helpful to investigate whether trends can be observed related to the perceived degree of difficulty of international market access of companies.

Furthermore, the design support tool has to be validated against more expert views to gain more perspectives on the tool and its implementations.

13. APPENDICES

Appendix A: Dutch Life Sciences and Health industry numbers



Figuur 10: Numbers on the amount of jobs, products, revenue, subsidies, capital and listed & non-listed companies

Appendix B: History and developments of the pharmaceutical & the biotechnology industry

The origin of the pharmaceutical industry can be found in the Middle Ages with apothecaries and pharmacies offering traditional remedies. However the industry of today finds its roots in the second half of the 19th century. The pharmaceutical industry started to develop between World War I and World War II (WWII) with two breakthrough discoveries, namely insulin and penicillin. Later, social health care systems were founded. An example of this is the UK based National Health Service (NHS) which was founded after WWII to safeguard patient's health care. A new amendment to the US FDA in 1962, requesting proof of efficacy of future medicines and an elaborate description of possible side effects, showed the increased concern for regulation.

The pharmaceutical industry experienced times of high drug development but with the arrival of the blockbuster drug *Tagamet* in 1977 a shift started to set in; a period of mainly sales-driven drug development. Competition started to rise and the companies started to realize that they had to interact more with their patients in order to stay competitive. Although an intensified market developed, breakthrough discoveries continued with large expenses and high levels of risk.

The pharmaceutical industry today consists of a wide range of companies. No only drug developing companies are part of this ecosystem but for example also Specialized Service Providers (SSPs) and Medical technology manufactures. SSPs consist of organizations for manufacturing drugs (contract manufacturing organizations, CMOs') or for clinical phase studies (contract research organizations, CROs). The development process of a medical product differs as some products do not have to be tested in clinical trials.

Besides the classical 'pharmaceutical industry' the 'biotechnology industry' has expanded in the late 20th and early 21st century. Scientists are currently able to make use of living cells to design new crops (green biotechnology), purify water quicker (blue biotechnology), to produce chemicals (white biotechnology) and produce complex biological medicines (red biotechnology). The fourth group, red biotechnology, shows overlap with the pharmaceutical industry as can be seen in Figure 11. Especially the pharmaceutical industry will be the domain of interest in this study and thus specialized service provider developing laboratory equipment, the biopharmaceutical and the diagnostic tool companies are considered in this study.

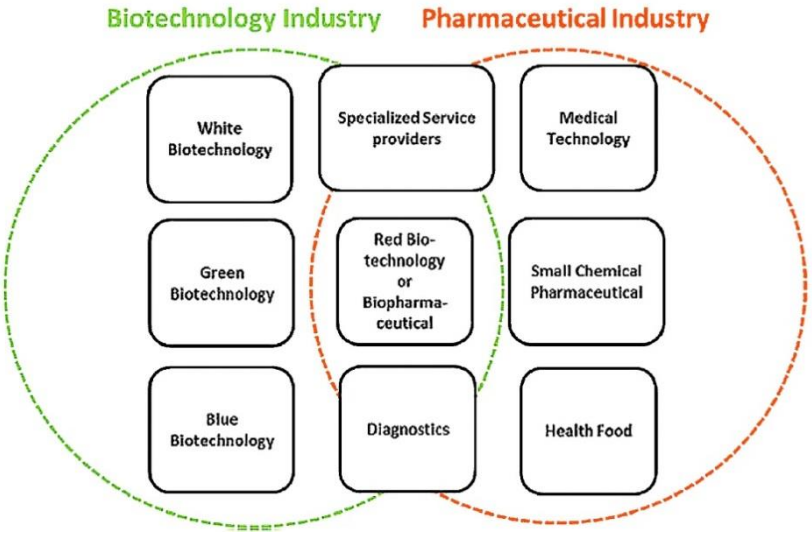


Figure 11: Schematic overview of the biotechnology and pharmaceutical industry which includes the overlapping areas

25 years of pharmaceutical and biotechnology industry in the Netherlands

The pharmaceutical sector is nowadays a highly international market. Regarding the R&D investments in medicines, the Netherlands do not play a significant role with a share of only 1 to 2 percent of the world market R&D investments. Although several companies in the Netherlands are concerned with research and development, the biggest part of the companies serve as sales units for multinationals.
Within the pharmaceutical sector the Netherlands do not have a substantial role. In the biopharmaceutical industry or the biotechnology industry, however, the Netherlands have a prominent position. Over the last years the biotechnology industry including the aforementioned green, blue, white and red biotechnology rapidly developed and an overview of the highlights of the last 25 years is provided (see the full overview of the last 25 years biotechnology in the Netherlands in Figure 12).

Among the highlights of the last 25 years, the establishement of the Nederlandse Industriële en Agrarische Biotechnologie Associatie (NAIBA) in 1988 has to be mentioned. It was founded to encourage biotechnological development, as it was thought to be of utmost importance. Moreover, in 1990 the company Pharming triggered heavy ethical discussions due to the birth of the first transgene bull in the world which was created by this company. In the following years many companies and institutions were founded in the Netherlands such as Keygene (1989), Galapagos (1999) and BioFarmind (1996). Within this period also numerous mergers and acquisitions took place such as the acquisition of Gist Brocades (1998) by Dutch State Mines (DSM), the purchase of Mogen by Zeneca (1997) and the merger of Novartis with the earlier-fused-AstraZeneca in 2000, which formed the company Syngenta and is currently prominent in the agribusiness in the Netherlands.
Additionally Organon was acquired by Schering-Plough in 2007 and later merged with Merck Sharp & Dohme (MSD). This acquisition and the merger involved job losses as will be touched upon later on.
The more recent years of the biotechnology industry comprise activities of the company Uniqure, that received approval in the EU for the first gene therapy product in the Western world (2012), Prosensa that made an IPO in 2013 and the acquirement of Profibrix by The Medicine Company in 2013. This shows that small companies now include mergers or acquisitions as a possible outcome of their strategic goals. According to NautaDutilth (2012) most Dutch biotechnology companies (60%) strive to develop medical products to reach clinical phase I or clinical phase II and subsequently agree upon an alliance with a big pharmaceutical company. Some biotechnology companies want to pursue an early takeover (buyout) and others, aim for an IPO (Kerkhof, 2012) although this is not a popular strategy. This could have implications for the companies that will be selected in this study as several companies may want to pursue a buy out and will not consider market access while others want to make an IPO and will differently reflect on market access.

The changes of the landscape of companies in the Netherlands as well the changes in the product landscape and more information are presented in *Appendix A: Recent realized innovations by Dutch companies.*

Another recent development this year was the development of HollandBIO a branche organization that was created after combining the organizations Niaba and BioFarmind. HollandBIO namely represents the small ventures. Nefarma, another interest group for pharmaceuticals with 38 members, is focused on the research and development of new medicines, however Nefarma's members are mainly the established firms in the Netherlands.

Figure 12: Overview of highlights in Pharmaceutical and biotechnology industry in the Netherlands over the last 25 years

(HollandBIO)

Appendix C: Details on formal and informal lobbying by the taskforce LSH EU Connect

Nederland in zicht
Hoe maakt de Nederlandse LSH-sector optimaal gebruik van Brussel - en andersom!

3.1 Internationale agenda – een schets
De komende jaren bieden verschillende momenten om invloed uit te oefenen op de Brusselse (en andere internationale) agenda's en de doorvertaling ervan in Nederland. In bijlage 5.2 is een tijdslijn opgenomen met belangrijke momenten. Grofweg kunnen deze worden ingedeeld in de volgende 'rubrieken':
1. De ijzeren agenda van Brussel zelf
    - o Formele lobby
    - o Informele lobby
2. De politieke agenda
3. De bredere internationale agenda

3.1.1 De ijzeren agenda van Brussel zelf
Centraal in deze ijzeren agenda staan de besluitvormingsprocedures voor nieuwe voorstellen, strategische programma's en werkprogramma's. Deze agenda biedt tal van mogelijkheden voor beïnvloeding. Hieronder wordt een onderscheid gemaakt in formele en informele lobby.

- *Formele lobby*

VWS en EZ zitten als adviseur in het programmacomité voor Gezondheid in KP7 (OCW en AgentschapNL zijn 'alternate'). De lidstaten pleiten voor een vergelijkbaar comité voor H2020. Daarnaast is het Agentschap NL als 'national contact point' of 'national focal point' direct betrokken bij allerlei operationele aspecten van deze
Europese planning. De betrokken medewerkers kunnen/moeten optimaal worden ingezet om de Nederlandse agenda in Brussel uit te dragen, en terug te koppelen aan het Nederlandse veld. Naast deze meer technische inbreng, bieden de verschillende beslisorganen in Brussel zelf (met de Raden voor Concurrentievermogen en Gezondheid) mogelijkheden voor beïnvloeding. Contacten met ambtenaren die betrokken zijn bij de voorbereiding van deze organen (m.n. bij de PV in Brussel) is dan ook cruciaal. Op 'lager' niveau kan Nederland zijn stem laten horen via de formele adviescommissies ('comitologie'), die vastzitten aan verschillende initiatieven. Zo kennen de verschillende JPI's en Joint Actions een eigen comitologie, heeft het EIP een stuurgroep en zijn enkele initiatieven (zoals ERICs en Artikel 185-initiatieven) zelfs zelfstandige entiteiten met een eigen bestuur. Het is belangrijk bewust te zijn van al deze organen, een goed beeld te hebben van de Nederlandse afvaardiging hierin en deze mogelijk strategisch te beïnvloeden. Bijlage 5.3 bevat een overzicht
van organen en Nederlandse afvaardiging. Overigens is het goed om op te merken dat de lobby op het fundamentele excellente onderzoek, dat via de European Research Council wordt gestimuleerd, zeer beperkt
is. Dit is echter ook niet het kanaal waarop deze notitie zich richt.

- *Informele lobby via EP, EC, Neth-ER en Europese organisaties*

Voor de informele lobby is het Europees Parlement een belangrijke instelling. De Commissie Industrie, Onderzoek en Energie (ITRE) en de Commissie Milieubeheer, volksgezondheid en voedselveiligheid (ENVI) zijn de relevante Commissies in het Europees Parlement die respectievelijk Europese onderzoekprogramma's en –beleid en gezondheidszorg behandelen. De Nederlandse Europarlementariërs die zitting hebben in deze Commissies zijn de eerste aanspreekpunten om de unique selling points van de Taskforce LSH EU Connect op de agenda te krijgen. Dit betekent de onderwerpen kenbaar maken, eventueel een 'breakfast meeting' organiseren met betrokken Europarlementariërs en via deze weg draagvlak creëren met gelijkgestemde partijen in andere lidstaten. Ook de lobby op de wetgevende initiator, de Europese Commissie, moet niet
worden onderschat. Met haar 22.000 ambtenaren (evenveel als de Gemeente Amsterdam) heeft de Europese Commissie als taak de 500 miljoen inwoners van de EU te bedienen. Met deze kleine capaciteit staat de Europese Commissie zeer open voor nieuwe ideeën en stellen ze het op prijs als

experts hun expertise naar Brussel brengen. Speciale aandacht verdient daarbij het positioneren van zogenaamde 'END-ers', gedetacheerde experts. Deze kunnen strategisch geplaatst worden en zijn zeer belangrijk voor de lobby van 'binnenuit'. De Nederlandse Permanente Vertegenwoordiging in Brussel kan bij deze informele lobby een belangrijke rol spelen. Zij hebben een breed netwerk en goede toegang tot informatie en personen. Zij hebben goed zicht op de individuele belangen en voorkeuren van Europarlementariërs en kunnen zo adviseren over de juiste insteek. Ook Neth-ER kan de nodige ondersteuning bieden in de informele lobby middels het organiseren van seminars rondom een bepaald thema dat onder relevante partijen en Europese instellingen onder de aandacht gebracht kan worden. Europese koepelorganisaties die hun zetel hebben in Brussel zijn ook belangrijke lichamen om te beïnvloeden. Vaak dienen dergelijke organisaties als een informele vertegenwoordiger van allerlei gelijkgestemde organisaties die erbij zijn aangesloten (bijvoorbeeld de European Society of Cardiology). De laatste, maar wel een van de belangrijkste mogelijkheid voor informele lobby is om Nederlandse coördinatoren van lopende Europese projecten op de unique selling points te identificeren. Deze coördinatoren worden door Brussel regelmatig geraadpleegd en zijn uitstekend in de gelegenheid om onze centrale boodschap in Brussel over te brengen.

3.1.2 De politieke agenda

Een van de belangrijkste momenten in de politieke agenda is het Nederlandse voorzitterschap, de eerste helft van 2016. Nederland is daarnaast ondersteunend bij de voorzitterschappen die volgen (Slowakije en Malta). Aangezien deze landen geen heel sterke 'track record' hebben op het terrein van onderzoek en innovatie, strekken de kansen voor Nederland om zich te profileren, en nieuw Europees beleid te entameren, zich tot voorbij 2016 uit.

3.1.3 De internationale agenda

Ook in de Wereldgezondheidsorganisatie zijn grote veranderingen gaande op het terrein van Global Health Research. Recent is besloten tot de oprichting van een Global Observatory for Health Research, waarmee een deel van de internationale agendasetting Geneve plaats zal vinden. Eind 2013 zal een eerste consultatieve plaatsvinden om een aantal prioritaire thema's te selecteren. Ditz al vooral de EU-agenda op het terrein van 'global health' en armoede gerelateerde ziekten beïnvloeden.
Ook het nieuwe rapport over 'Priority Medicines for Europe and the World' van de WHO, zal van invloed zijn op de agenda van H2020 en IMI in het bijzonder (Ondersteuningsgroep LSH-EU Connect, 2014).

Appendix D: Appraisal process of the drug Xofigo

NICE, the health care guidance body has issued a new draft guidance on the 24th of March 2014 that is not recommending the use of radium-223 dichloride (Xofigo) for treating adults with hormone relapsed prostate cancer, symptomatic bone metastases and not known visceral metastases. The NICE Chief Executive, Sir Andrew Dillon, stated: "*At the beginning of the appraisal process, NICE works with stakeholders to identify the most appropriate treatments for the new drug to be compared. Clinical specialists told the committee that radium-223 would be used as an alternative treatment option to docetaxel as an initial treatment, and abiraterone as a second-line treatment when the disease has progressed. However, Bayer did not to provide the Committee with any data on how well radium-223 works compared to docetaxel or abiraterone or, only comparing it to placebo."* This highlights the importance of comparator studies. Furthermore Dillon continued: "*Bone metastases are very distressing for patients and their families, particularly as a result of bone pain and fatigue, which have a profound effect on patients' quality of life, by limiting their mobility and meaning full-time care would often be needed for daily activities. We know how important this could be to patients and we are disappointed not to able to recommend this drug, but we have to be confident that its benefits justify its considerable cost."* (GlobalData, 2014) This has direct indications for reimbursement within the UK and indirectly for other countries in Europe such as Germany.

The medicine did gain approval in the US and in Spain and has been launched in both countries in 2013 (GlobalData, 2014). Therefore approval in one country does not imply reimbursement assurance in other countries (Backhouse et al., 2011).

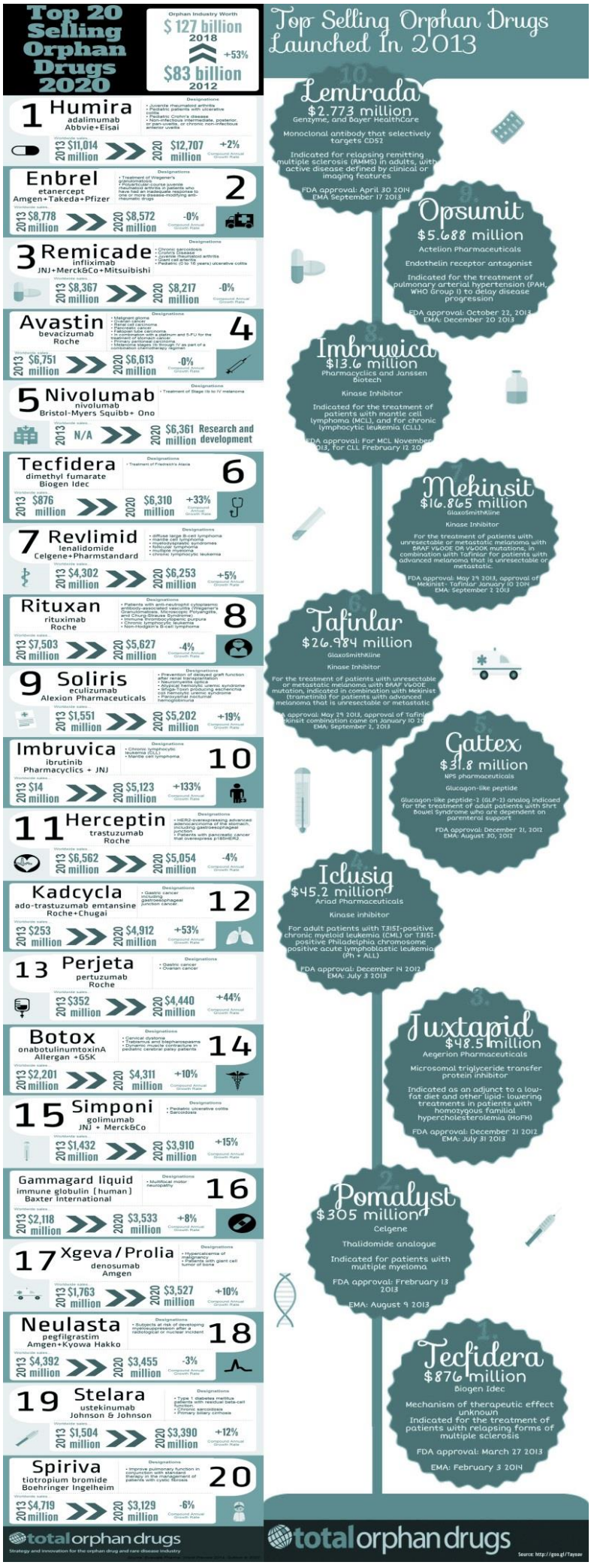
Appendix E: Outrageous pricing of the drug Solvadi

A new product Sovaldi, a Hepatitis C drug from the company Gilead Sciences, has come under fire from insurers and the Congress in the US, because the treatment price of $84.000 is 'outrageous'. This medicine is seen as a breakthrough treatment that will cure a majority of the Hepatitis C patients. Analysts project sales for Sovaldi to be $9.1 billion in 2017, according to Thomson Reuters Pharma. The company argues that the medicine will create huge savings over time for the health care system because it prevents complications from liver disease and transplants. Dr. Sharon Levine, associate director of the Permanente Medical group stated that: "*It's because this is a therapy that represents a substantial improvement over existing therapies… It's an outrageous price for a therapy that has huge public health implications*." However as the US health care spending is under scrutiny and President Barack Obama's Affordable Care Act strives to make health coverage accessible to everybody the market addition of a $1.000-a-pill provokes questions on medicine pricing (Beasley, 2014).

Appendix F: LSH sector map of the opportunities with the US

Prioriteitsland: Verenigde Staten	
	Mogelijke actie/ ondersteuning overheid
A. Markt (afzet goederen en diensten)	
Meest kansrijke subsectoren	
LSH-breed, o.m.: - Medische technologie en hulpmiddelen (medical devices) - Mobiliteitsoplossingen - Ziekenhuisbouw - Medische Kennis - E-Health - Biomaterialen - Onderzoeksapparatuur	Focus: Massachusetts, California, Illinois, North Carolina, New Jersey, New York, Indiana Incl. afzet bij WB/VN.
	Ondersteuning overheid (t.b.v. alle subsectoren): - Vraagbeantwoording en advisering aan bedrijven. - Matchmaking. - Organisatie van missies en evenementen. Bijv. paviljoen op Bio International (Chicago, april 2013), Lab on a Chip World Congess (California, 2013). - Facilteren publiek-private partnerschappen (bijv. via PIB-Partners for International Business van AgentschapNL). - Marktverkenning door postennetwerk. - Positionering bedrijven voor WB/VN-tenders.
B. Technologische samenwerking	
Meest kansrijke kennisgebieden	
Personalized medicine	Focus: California, Massachusetts
Healthy ageing	Focus: California, Washington DC, Massachusetts
E-Health	Focus: Massachusetts, California, North Carolina, Maryland
Medische technologie	Focus: Massachusetts, Illinois, California
	Ondersteuning overheid (t.b.v. alle kennisgebieden hierboven): - Vraagbeantwoording en advisering aan kennisinstellingen. - Scouting van R&D trends en ontwikkelingen in innovatie- en ondernemerschapsbeleid. - Organisatie van missies en evenementen. - Strategische samenwerking met Boston, bijvoorbeeld via matchmakingsprogramma MassBio en het LSH platform in NL. - Aansluiting bij communicatie zoals Holland Branding, publieksdiplomatie. - Rapportage en informatieverstrekking (bijv. artikelen). - Netwerken.
C. Acquisitie (aantrekken van investeringen die Topsector in NL versterken)	
Meest gewenste subsectoren	
Rode Biotech/medical Diagnostics & Imaging Medische apparatuur/ systemen (nanomedicine, Photonics, Printing, Robotics & Embedded Systems, Imaging, E- Health) Regenerative medicine Onderzoeksgebieden: - Translational Research - Clinical Research - Cardiovascular Research - Infectious Diseases - Oncology - Rheumatology - Neurodegenerative Diseases	Ondersteuning overheid t.b.v. alle subsectoren hiernaast. Steun aan geïnteresseerde bedrijven bij: - Lead Generation (samen met regionale partners/life sciences netwerk in Nederland). - Informatieverschaffing. - Begeleiding. - Netwerken. - Presentaties, promotie van Nederland (de keus voor Nederland binnen Europa). - opzet van een bedrijf in Nederland inclusief vestigingslocatie keus in samenwerking met regionale partners. - ondersteuning gericht op type activiteit van outsourced distributie (samen met NDL) - Marketing & Sales - R&D - Hoofdkantoren. - Investor Relations - steun aan bestaande buitenlandse bedrijven om Nederland to verkopen voor uitbreiding, consolidatie, nieuwe activiteiten etc.

Appendix G: Top selling orphan drugs 2020 en launched in 2013



Appendix H: Conceptual model construct factors

Construct Factors
Product factors
Product characteristics Meet the target product profile requirements for clinical usage such as dosage, safety, side effects, quality of life to meet the requirements Define the value proposition (clinical value, patient value, economic value) Lack of "breakthrough designation" (preventing a quick market entry)
Comparators Current on the market medicines (direct comparators) Current pipeline medicines (indirect comparators)
Pricing Define appropriate pricing
Reimbursement Meet the reimbursement requirements
Firm specific factors
Financial capital Availability of financial capital
Absorptive capacity Age Size Management's international business experience (years) Management's international business experience (difference in countries) Management abilities Employees abilities
Access to distribution network & promotion capacity Access to distribution network and channels Lobbying Negotiation Creating awareness (e.g. patients societies)
Sector specific factors
Demographic trends Market size
Legislation Too strict national regulations in certain aspects Lack of incentives for funds/grants Too regulated national or international prescription guidelines
Stakeholders Payers influence Patients influence Key opinion leaders influence
HTA application Meet health technology assessment (if required for coverage and/or reimbursement in a country)

Market Access Barriers and Strategies (MABS) Survey 2014 TU Delft, Technology, Policy and Management

Dear Sir/Madam (please fill in),

By answering the questions you, as a chief or director, support us in gaining a better understanding of barriers to market access of advanced medicines and diagnostics, and in strategies to overcome these barriers.

- Your response will be kept strictly confidential
- Please answer the questions and mail the document.
- The headlines of the results will be mailed to you in a small report August this year.

Many thanks in advance!
Sincerely yours,
Prof. dr. Marina van Geenhuizen and Charlotte de Jonge. For information: 015-2786729 or m.s.vangeenhuizen@tudelft.nl

Questions:

1. a. What is your job description? O Chief executive officer O C-level officer O Manager O Otherwise: .....
   b. What is your job field? O Business development O Marketing O Corporate O Otherwise:.....
2. For how many years do you work in this company? ..... years
3. Number of employees in 2013 (Full Time Equivalent) .....
4. Turnover class in 2013 (Euro): O <100.000; O 100.001 – 500.000; O 500.001 – 1.000.000; O 1.000.001 –5.000.000; O More
5. From discovery to market
   a. In which stage(s) is the *main product* of the company? Please, tick below.
   O Discovery research O Phase I O Phase II O Phase III O Regulatory review O Phase IV O Pre-registration
   b. Your company may have more products: What is/are the main *product's indication*(s) (e.g. leukemia, breast cancer, arthritis):
   .....
6. Experience of the management team:
   a. The member with most business experience: how many years of experience does he/she have in the sector? ..... years
   b. The member with most international business experience: how many years of *international* experience does he/she have in the sector? ..... years
   c. related to 6b, what are his/her main countries of experience (mention the main three)? .....
7. Please describe briefly the main problem/challenge in market access for this company? .....
   .....
8. How do you perceive the gaining of market access for the *company's main product*? Please tick the box that matches your experience:
   O Very problematic O Problematic O Neutral O Easy O Very easy

9. Please tick the boxes for each barrier, regarding importance in market access and gravity of barriers to market access of the *main product*.

Potential barrier	**Importance for market access (runs 1 to 5)** 1 = not important and 5 = highly important 1	2	3	4	5		**Gravity of barrier to market access (runs 1-5)** 1 = very small while 5 = very large gravity 1	2	3	4	5
Meet the target product profile requirements for clinical usage such as dosage, safety, side effects, quality of life											
Currently on the market medicines (direct comparators)											
Currently pipeline medicines (indirect comparators)											
Define the value proposition (clinical, patient and economic value)											
Define appropriate pricing											
Meet the reimbursement requirements											
Lack of "breakthrough designation" (preventing a quick market entry)											
Otherwise (please describe):											
Effective lobbying											
Effective negotiation											
Creating awareness (e.g. patients societies)											
Availability of financial capital											
Access to distribution network and channels											
Lack of risk-sharing agreements											
Employees abilities											
Management team abilities											
Otherwise (please describe):											
Market size											
Too strict national regulations in certain aspects											
Lack of financial incentives such as funds/grants (e.g. Innovation credit)											
Too regulated national or international prescription guidelines											
Payers influence											
Patients influence (excluding payers)											
Key Opinion Leader's influence											
Meet the health technology assessment (if required for coverage and/or reimbursement in a country)											
Otherwise (please describe):											

10.Mention your two most pressing barriers: (1) ..... (2) .....
What solution would you suggest for each of them? (1)..... (2) .....

Appendix I2: Short version of the MABS survey

Dear…..,

Hopefully, by using a short version of our survey below you, as a chief or director, will support us in gaining a better understanding of barriers to market access of advanced medicines and diagnostics, and in strategies to overcome barriers.

· Your response will be kept strictly confidential
· Please, answer the questions below in 5 minutes.
· The headlines of the results will be mailed to you in a small report August this year

Many thanks in advance!
Sincerely yours,
Prof. dr. Marina van Geenhuizen and Charlotte de Jonge.

Questions:
1. Number of employees in 2013 in the company (Full Time Equivalent): ……

2. Turnover class in 2013 (Euro): O <100.000; O 100.001–500.000; O 500.001–1.000.000; 1.000.001–5.000.000; O More

3. From discovery to market. In which stage is the main product of the company?
O Discovery research O Phase I O Phase II O Phase III O Regulatory review O Phase IV O Pre-registration

b. Your company may have more products: What is/are the main product's indication(s) (e.g. leukemia, breast cancer, arthritis):
……

4. How many members of the Management Team have more than 5 years international experience abroad in the sector? …… members

5. Please describe briefly the main problem/challenge in market access for your company?
……
6. How do you perceive the gaining of market access for the company's main product? Please tick the box that matches your experience:
O Very easy O Easy O Neutral O Problematic O Very problematic

7. Please rate the gravity of barriers for your company to market access of the main product.

Potential entry barrier	**Gravity runs from 1-5** 1 = very small while 5 = very large gravity 1	2	3	4	5
Meet the target product profile requirements for clinical usage such as dosage, safety, side effects, quality of life					
Currently on the market medicines (direct comparators)					
Currently pipeline medicines (indirect comparators)					
Define the value proposition (clinical, patient and economic value)					
Define appropriate pricing					
Meet the reimbursement requirements					
Lack of "breakthrough designation" (preventing a quick market entry)					
Otherwise (please describe): ……..					
Effective lobbying					
Effective negotiation					
Creating awareness (e.g. patients societies)					
Availability of financial capital					

Access to distribution network and channels					
Lack of risk-sharing agreements					
Management team abilities					
Otherwise (please describe): …….					
Market size					
Too strict national regulations in certain aspects					
Lack of financial incentives such as funds/grants (e.g. Innovation credit)					
Too regulated (inter)national prescription guidelines					
Payers influence					
Patients influence (excluding payers)					
Key Opinion Leader's influence					
Meet the Health Technology Assessment (if required)					
Otherwise (please describe): …….					

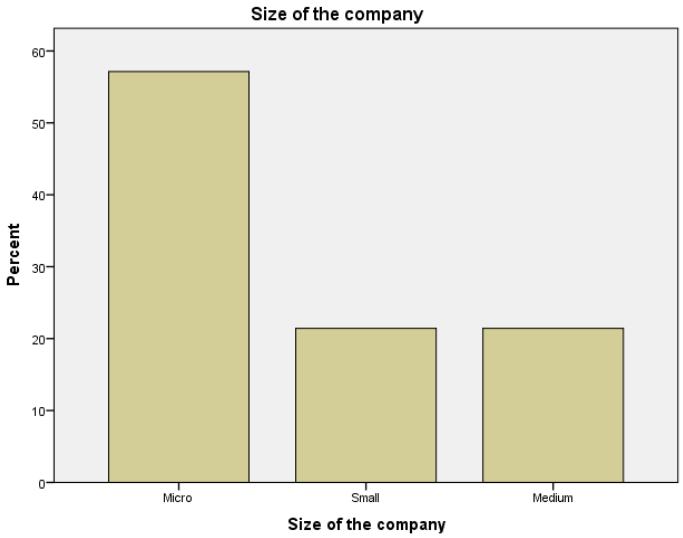
Thanks again!

Appendix J: Characteristics of the respondents

Size

Statistics		
Size of the company		
N	Valid	14
	Missing	0
Mean		1,64
Std. Deviation		,842

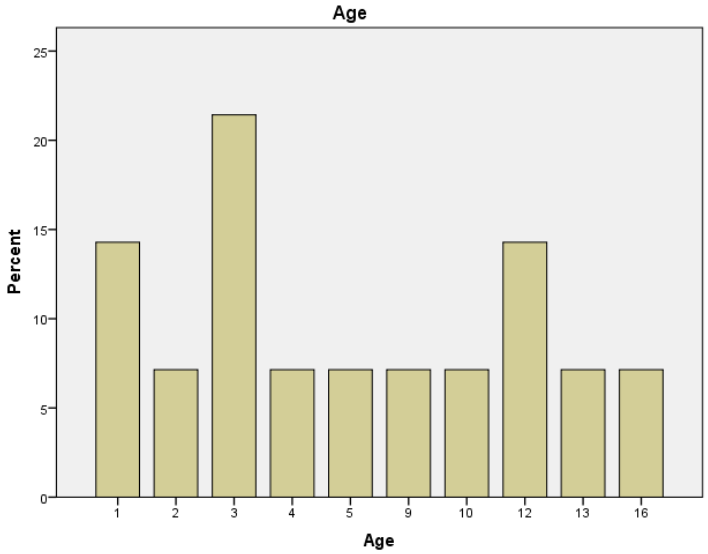
Size of the company					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Micro	8	57,1	57,1	57,1
	Small	3	21,4	21,4	78,6
	Medium	3	21,4	21,4	100,0
	Total	14	100,0	100,0	



Age

Statistics		
Age		
N	Valid	14
	Missing	0
Mean		6,71
Std. Deviation		5,090
Minimum		1
Maximum		16

Age					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	14,3	14,3	14,3
	2	1	7,1	7,1	21,4
	3	3	21,4	21,4	42,9
	4	1	7,1	7,1	50,0
	5	1	7,1	7,1	57,1
	9	1	7,1	7,1	64,3
	10	1	7,1	7,1	71,4
	12	2	14,3	14,3	85,7
	13	1	7,1	7,1	92,9
	16	1	7,1	7,1	100,0
	Total	14	100,0	100,0	



Product phases

Discovery phase					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Discovery	10	71,4	71,4	71,4
	No discovery	4	28,6	28,6	100,0
	Total	14	100,0	100,0	

Phase I					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Phase I	5	35,7	35,7	35,7
	No phase I	9	64,3	64,3	100,0
	Total	14	100,0	100,0	

Phase II					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Phase II	7	50,0	50,0	50,0
	No phase II	7	50,0	50,0	100,0
	Total	14	100,0	100,0	

Phase III					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Phase III	3	21,4	21,4	21,4
	No phase III	11	78,6	78,6	100,0
	Total	14	100,0	100,0	

Regulatory review					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Regulatory review	2	14,3	14,3	14,3
	No regulatory review	12	85,7	85,7	100,0
	Total	14	100,0	100,0	

Phase IV					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No phase IV	14	100,0	100,0	100,0

Marketed					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Marketed	1	7,1	7,1	7,1
	Not marketed	13	92,9	92,9	100,0
	Total	14	100,0	100,0	

Appendix K: RSDAs approximations, frequencies of attributes and core attributes

RSDA 1

Table 14: Approximations

Approximations	# of Objects	Upper level	Lowel level
1	0	0	0
2	2	2	2
3	4	4	4
4	4	4	4
5	4	4	4
Quality of classification			1

The quality of the classification shows the highest score namely 1, so the next step attribute reduction is possible. This step is used to form all combinations of condition factors that can completely determine the variation in international market access. The frequencies can be found in Table 15.

Table 15: Frequency of attributes, reducts and core

Attributes	Frequency	
	Number	%
C1	26	27.03
C2	10	35.14
C3	13	51.35
C4	19	29.73
C5	11	37.84
C6	14	35.14
C7	13	29.73
C8	21	56.76
C9	14	37.84
C10	26	70.27
Core: no		

Table 16: Summary of the rough set analysis

Condition attribute	Overall frequency in rules
C1: Size	0
C2: Product type	1
C3: TPP	2
C4: Pricing	1
C5: Reimbursement	4
C6: Creating awareness	0

C7: Financial capital	3
C8: Management	5
C9: Regulations	3
C10: Risk agreements	

Indicators of strength of the information table

Number of core factors	1 out of 9
Quality of the core	1.0

Indicator of strength of the results

Maximal coverage of rules	14.3%
Majority of coverage (7)	7.1%

RSDA 2

Table 17: Approximations

Approximations	# of Objects	Upper level	Lowel level
1	0	0	0
2	2	2	2
3	4	4	4
4	4	4	4
5	4	4	4
Quality of classification			1

Table 18: Frequency of attributes, reducts and core

Attributes	Frequency	
	Number	%
C11	1	100.00
C8	1	100.00
Core: C11, C8		

Condition attribute	Overall frequency in rules
C1: Size	1
C11: Age	10
C8: Management team	6

Indicators of strength of the information table

Number of core factors	1 out of 3
Quality of the core	1.0

Indicator of strength of the results

Maximal coverage of rules	14.3%
Majority of coverage (7)	7.1%

14. REFERENCES

G. Ahuja, R. Katila, (2001). Technological acquisitions and the innovation performane of aquiring firms: A longitudinal study. *Strategic Management Journal, 22*, 197-220.

T. Andersson et al., (2010). Bio-pharma: a financialized business model. *Critical Perspectives on accounting*, Vol 1. (7) p. 631-641.

D. Armstrong, (2014, April 24). Miljardenspel versterkt markmacht farmaceuten. *NRC Handelsblad*, p. E4.

M. Backhouse et al., (2011). Early dialogue between the developers of new technologies and pricing and reimbursement agencies: a pilot study. *Elsevier Inc. - Value in Health*, 608-615.

J. Bailey, J. Burch, M. Burch (2010). *Twenty-five essential skills & strategies for the professional behavior analyst.* New York: Routledge Publishing.

H. Barkema, F. Vermeulen, (1998). Inernational expansion through start-up or acquisition: A learning perspective. *Academy of Management Journal, 41*, 7-26.

D. Beasley, (2014, April 2). *Exclusive: Costs to public of $84,000 hep C drug 'outrageous' - Kaiser* . Opgeroepen op June 3, 2014, van Reuters: http://www.reuters.com/article/2014/04/02/us-hepatitisc-gilead-sciences-idUSBREA311Y120140402

M. Becker, M. Lillemark, (2006). Marketing/R&D integration n the pharmaceutical industry. *Research policy, 35*, 105-120.

P. Bierly, A. Chakrabarti, (1996). Generic knowledge strategies in the U.S. pharmaceutical industry. *Strategic Management Journal, 17*, 123-135.

E. Bower, D. Hurry, (1993). Strategy through the option lesn: An integrated view of resource investments and the incremental-choice process. *Academy of Management Review, 18*, 760-782.

NOS (Componist). (2014). Farmaceutische industrie moet zich specialiseren. [R. v. Brink, Uitvoerend artiest, & NOS, Dirigent] Netherlands.

K. Bruin, (2014, June 30). Market access barriers. *CardioGenx/SkylineDx*.

CADTH. (2009). *CEDAC final recommendation on reconsideration and reasons for recommendation: dabigatran etexilate.*

Capgemini Consulting. (2009, October). Leveraging succes factors fo market access in the Life Sciences Industry. *Cegedim Dendrite*, 1-8.

CBS Statline. (sd).

J. Chambers, P. Neumann, (2010). US healthcare reform: implications for health economics and outcomes research. *Expert Rev. Pharmacoecon. Outcomes Res.*, Vol 10. p215-216.

D. Chaya, (2005, Jan). Survival strategies for start-ups. *Journal of commercial biotechnology, 11*(2), 130-133.

S.E. Christensen, (2012). Chapter 2: From a Micro–Macro Framework to a Micro–Meso–Macro Framework Bocong Li. In S. e. Christensen, *Engineering, development and philosphy: American, Chinese and European perspectives* (p. 412). Springer.

I. Cockburn, (2004). The changing structure of the pharmaceutical industry. *Health affairs, 21*(1), 10-22.

W. Cohen, D. Levinthal, (1989). Innovation and learning: The two faces of R&D. *Economic Journal*(99), 569-596.

W. Cohen, D. Levinthal, (1990). Absorptive capacity: A new perspective on learning and innovation. *Administrative Science Quarterly*(35), 128-152.

Commisie Doek. (2009). *Advies medisch-wetenschappelijk onderzoek met kinderen.*

J. Cook, (2001). Practical guide to medical education. *Pharmaceutical marketing*, pp. 14-22.

E. David, T. Tramontin, R. Zemmel, (2010, February). The road to positive R&D returns. *McKinsey Quarterly*.

J. DiMasi et al. (2003). The price of innovation: new estimates of drug development costs. *Journal of health economics, 22*, 151-185.

M. Drummond et al., (2008, July 4). Key principles for improved conduct of health technology assessment for resource allocation decisions. *International Journal of Technology Assessment in Health Care, 24*(3), 244-258.

M. Drummond, A. Towse, (2014, January). Orphan drugs policies: a suitable case for treatment. *European Journal of Health Economy*.

EFPIA. (2014, March 10th). *Reimbursement in European markets.* (M. A. Edith Frénoy – Director, Uitvoerend artiest) Turin, Turin.

H. Ellis, (1965). *The transfer of learning.* New York: Macmillan.

Ernst & Young. (2014). *Commercial excellence in Pharma 3.0.* Opgeroepen op April 08, 2014, van Ernst & Young: http://www.ey.com/GL/en/Industries/Life-Sciences/EY-commercial-excellence-in-pharma-3-0

Estes. (1970). *Learning theory and metal development.* New York: Academic Press.

Eurorids. (2014, March 18). *Eurordis Rare Diseases Europe.* Opgeroepen op July 2, 2014, van Orphan Medicines Regulation: http://www.eurordis.org/content/promoting-orphan-drug-development

Eyeforpharma. (2014). *Industry Healtcheck 2014: Testing the health of the pharmaceutical industry.* Eyeforpharma.

A. Fano, (2000). *What's wrong with Xeno*. Opgeroepen op August 08, 2014, van Campaign for responsible transplantation: http://www.crt-online.org/wrong.html

E. Faulkner et al., (2012). Challenges in the development and reimbursement of personalized medicine - payer and manufacturer perspectives and implications for health economics and outcomes research A report of the ISPOR personalized medicine special interest group. *Elsevier Inc. Value in Health 15*, 1162-1171.

E. Faulkner, (2012). Challenges in the development and reimbursement of personalized medicine-payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR personalized medicine special interest group. *Value in health, 15*, 1162-1171.

FDA, (2014, May 29). *Regulatory information: Fact Sheet: Breakthrough Therapies.* Opgeroepen op June 3, 2014, van FDA U.S. Food and Drug administration: http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm329491.htm

J. Froud et al., (2006). *Financialisation and strategy, narrative and numbers.* Londen: Routledge.

D. Garde, (2014, Jan 22). *U.K. mulls a 'breakthrough' drug program of its own Read more: Breakthrough Therapy - FierceBiotech http://www.fiercebiotech.com/tags/breakthrough-therapy#ixzz35Z7Mh0bP Subscribe at FierceBiotech.* Opgeroepen op June 24, 2014, van FierceBiotech: http://www.fiercebiotech.com/story/uk-mulls-breakthrough-drug-program-its-own/2014-01-22

S. Garrett, (2002, June). 11 steps to succesful market planning. *Pharmaceuical executive's successful product management supplement*.

A. Gawande, (2009). *The Checklist Manifesto.* Metropolitan.

C. Gispen-de Wied, (2013). From molecule to market access: Drug regulatory science as an upcoming discipline. *European Journal of Pharmacology 719*, 9-15.

P.E. Gleadle, (2012). Restructuring and innovatoin in pharmaceuticals and biotech: the impact of financialisation. *Cricital perspectives on accounting, 25*, 67-77.

GlobalData, (2014, April 02). *View Product Overview*. Opgeroepen op June 03, 2014, van GlobalData Pharma eTrack: http://www.pharmaetrack.com/ProductsView.aspx?ProductType=0,1&ProductID=11452

GlobalData, (2014, March 24th). *NICE unable to give the go ahead to new prostate cancer drug in preliminary recommendations.* Opgeroepen op May 28, 2014, van GlobalData Pharma eTrack: http://www.pharmaetrack.com/NewsDetails.aspx?ArticleID=DNiX5h@b5q8yQogpr4Cc@A==&type=M

J. Gottlieb et al., (2013). Infomation-seeking, curiosity and attention and neural mechanisms. *Trends in Cognitive Sciences, 17*(11), 585-593.

B.H. Gottsch, (2014). *Don't Leave Love to Luck: Designing to Influence With Health Apps*. Opgeroepen op April 22, 2014, van EYEforpharma: http://uk.eyeforpharma.com/fc_eyeforpharmalz/lz.aspx?p1=05697114S5224&CC=&p=1&cID=0&cValue=1

Government of the Netherlands, (2014, APril 16th). *Entrepreneurship and innovation: life sciences and health.* Opgehaald van Government of the Netherlands: http://www.government.nl/issues/entrepreneurship-and-innovation/investing-in-top-sectors/life-sciences-and-health

R. Gramzow et al., (2003). Self-evaluation bias and academic performance: Some ways and some reasons why. *Journal of research in personality*(37), 41-61.

A. Gülümser, P. Nijkamp, (2009). Embeddedness of Entrepreneurs in Rural Areas: A Comparative Rough Set Data Analysis. *Tinbergen Institute Discussion Paper, 058*(3).

C. Haslam et al., (2011). *UK bio-pharma: Innovation, re-invention, and capital at risk.* Edinburgh: The institute of chartered accountants of Scotland.

HollandBIO, (2014). *Biotechnologie.* Opgeroepen op June 10, 2014, van HollandBIO: http://www.hollandbio.nl/biotechnologie

HollandBIO, (2014, July 11). *Enthousiasme over extra krediet.* Opgeroepen op July 18, 2014, van HollandBIO: http://www.hollandbio.nl/nieuwsberichten/enthousiasme-over-extra-krediet

HollandBIO, (2014, June 10). *Financiering grootste uitdaging voor het life sciences MKB.* Opgeroepen op June 23, 2014, van HollandBIO: http://www.hollandbio.nl/nieuwsberichten/financiering-grootste-uitdaging-voor-het-life-sciences-mkb

J. Hughes et al., (2003). *Analysis of the risks embedded in asymmetrical alliances in the pharmaceutical industry.* Northwestern: Kellog School of Management.

M. D. Hynes Iii, (2009, december). Project and capacity management: An application to drug development. *Computers and chemical engingeering, 33*, 1994-1998.

M. Jackson, (2014, February 28). *Pharma-biotech collaborations: eigth themes from Biocom's partnering conference.* Opgeroepen op July 9, 2014, van Scipt intellegence:

http://www.scriptintelligecnce.com/home/Pharma-biotech-collaborations-Eigth-themes-from-biocoms-partnering-conference

J.Jansen et al., (2005, Dec). Managing potential and realized absorptive capacity: how do organizational antecedents matter? *The Academy of Management Journal, 48*(6), 999-1015.

F. Janus et al., (2008). *The eye of the storm.* McKinsey & Company. McKinsey & Company.

C. Jommi et al. (2012). Market access management by pharmceutical companies in a complex environment: The italian case study. *Journal of medical marketing, 12*(2), 93-103.

Kantar Health, (2014). *Market access.* Opgeroepen op April 08, 2014, van Kantar Health: http://www.kantarhealth.com/kantar-health-spotlights/market-access

J. Kerkhof, (2012). Dutch biotech companies: from start-up to exit. *Life Sciences Outlook 2012.* NautaDutilh.

L. Kim, (1998). Crisis construction and organizational learning: Capability building in catching-up at Hyundai Motor. *Organization Science, 9*, 506-521.

E. Kolassa, (1995). Physicians' perceptions of pharmaceutical prices: their accuracy and effect on the prescribing decision. *Journal Res Pharmaceutical Economics, 6*(1), 23-27.

E. Kolassa, (2009). *The strategic pricing of pharmaceuticals.* United States of America: The PondHouse Press.

A. Kudrin, (2012, Dec 7). Overview of the biosimilars: Strategic considerations of various issues. *Journal for the generic medicines sector, 9*(4), 187-206.

L. de Jong. (2013, 08 14). *Prioriteitslanden Overzicht.* Opgeroepen op August 04, 2014, van Topsectoren.nl: http://topsectoren.nl/documenten/life-sciences-health/LSH-13-040-LSH-prioriteitslanden-v4_2013-10-01_34.pdf

P. Lane et al., (2001). Absorptive capacity, learning, and performance in international joint ventures. *Strategic Management Journal, 22*, 1139-1161.

P. Lane et al., (2006). The reification of absorptive capacity: A critical review and rejuventation of construct. *Academy of Management Review, 31*(4), 833-863.

P. Lane, M. Lubatkin, (1998). Relative absorptive capacity and interorganizational learning. *Strategic Management Journal, 19*, 461-477.

Life Sciences & Health, (2011, June 1). *Topsectorplan Life Sciences and Health.* Opgeroepen op August 4, 2014, van MKB.nl: http://www.mkb.nl/images/rapport-topsector-life-sciences-health.pdf

Life Sciences and Health Sector. (2011). *New Biology, Sectorplan Nieuwe Biologie, het kloppend hart van de life sciences.*

T. Lonngren, (2010, July). *Successes and challenges in drug development - a regulatory perspective.* (T. Lonngren, Uitvoerend artiest) 16th World Congress on Basic and Clinical Pharmacology, Copenhagen, Denmark.

L. Lupo, (2014, May 14). *Has orphan drug pricing reached a breaking point?* Opgeroepen op June 4, 2014, van Total orphans drugs: http://www.orphan-drugs.org/2014/05/14/orphan-drug-pricing-reached-breaking-point-find-prometic-say/?utm_campaign=Total%20Orphan%20Drugs%20content%2003062014.html&utm_medium=email&utm_source=Eloqua#sthash.2IrFrGq7.dpbs

J. Marchant, (2010). *New approaches to gaining market access for pharmaceuticals.* SCRIP. Business Insights.

S. McGrath, (2010). Market access - an essential investment before drug launch. *Journal of Commercial Biotechnology 16*, 201-205.

S. Morgen et al., (2008). Towards a definition of pharmaceutical innovation. *Open Med.*, Vol 2. e4-e7.

D.Mowery et al., (1996). Strategic alliances and interfirm knowledge transfer. *Strategic Management Journal, 17*, 77-91.

R. Moynihan, (2008, June 21). Key opinion leaders: independent experts or drug representatives in disguise? *British Medical Journal, 336*(7658), 1402-1403.

Nederlandse Vereniging voor Kindergeneeskunde, (2012, June). Zorgvuldigheidscriteria rond onderzoek bij kinderen. *Kinderarts en wetenschap*, pp. 56-57.

P. Neumann et al. (2008). Medicare's national coverage decisions for technologies, 1999-2007. *Health Aff.*, Vol 27; p. 1620-1631.

NFU, (2011, May 10). *Reactie NFU op plannen topteam Life Sciences*. Opgeroepen op August 2014

F. van Nooten, (2012, June). Health economics and outcomes research within drug development. Challenges and opportunities for reimbursement and market access within the bioparhma research. *Drug discovery today, 17*, 615-622.

Novartis, (2014, April 22). *Novartis announces portfolio transformation, focusing company on leading businesses with innovation power and global scale: Pharmaceuticals, Eye Care and Generics.* Opgeroepen op June 10, 2014, van Novartis: http://www.novartis.com/newsroom/media-releases/en/2014/1778515.shtml

Nyenrode Business University, (2009). *Biotech SME inquiry.* Nyenrode Business University.

Ondersteuningsgroep LSH-EU Connect, (2014, February 12). *Nederland in zicht. Hoe maakt de Nederlandse LSH-sector optimaal gebruik van Brussel- en andersom!* Opgeroepen op August 4, 2014, van topsectoren.nl: http://topsectoren.nl/documenten/life-sciences-health/Actieplan-Life-Sciences-Health_2014-02-12_97.pdf

Z. Pawlak, (1991). *Rough Sets.* Dordrecht: Kluwer.

Z. Pawlak, (2001). AI and intellligetn industrial application: the rough set perspective, . *Cyb. Syst. Int. J.*(31), 227-252.

PBAC, (2006). *Public Summary Document: Nicotinic Acid.*

M. Pelletier, (1999). *The managerial decision-marking process fith edition.* Opgeroepen op August 04, 2014, van College Cengage: http://college.cengage.com/business/harrison/managerial/5e/onstructors/index.html

P. Pesanello et al., (2010). Market Access, are you really ready? *Journal of Medical marketing: device, diagnostic and pharmaceutical marketing*, Vol 10; p.25-35.

L. D. Pillis, (2014, February 6). *Drug companies have always been bad at collaboration. That's changing.* Opgeroepen op July 9, 2014, van Washington Post: http://www.washingtonpost.com/blogs/wonkblog/wp/2014/02/06/drug-companies-have-always-been-bad-at-collaboration

W. Powell et al., (1999). *Network Position and Firm Performance: Organizational Returns to Collaboration in the*. Opgeroepen op August 2014, van Stanford University: http://www.stanford.edu/~woodyp/papers/Rso1.pdf

D. Power, (2003, May 31). *A brief history of decision support systems DSS version 2.8.* Opgeroepen op August 5, 2014, van www.dssresources.com: http://www.marbef.org/wiki/Decision_support_tools#cite_note-Power-3

D. Power, (2005). *Communications-driven DSS.* Opgeroepen op August 2014, van www.dssresources.com: http://www.dssresources.com/dsstypes/cdss.html

D. Power, (2005). *Knowledge-driven DSS.* Opgeroepen op August 2014, van www.dssresources.com: http://www.dssresources.com/dsstypes/kddss.html

D. Power, (2007, May). *Ch.10 Building knowledge-driven DSS and mining data.* Opgeroepen op August 2014, van www.dssresources.com: http://www.dssresources.com/subscriber/password/dssbookhypertext/ch10/page4.html

PriceWaterhouseCoopers, (2009). *Pharma 2020: Marketing the future, Which path will you take?* PriceWaterhouseCoopers.

F. Raaphorst, (2012). *Biopharmaceutical industry sector report.* Rabobank international corporate clients.

P. J. Rankin, (2003). Chapter 2 of the pharmaceutical pricing compendium. In C. R. Associates, *Global pricing strategies for pharmaceutical product launches* (pp. 1-7). URCH publishing.

B. Reisetter et al., (2005). Relationship between psychosocial physcian characteristcs and physician price awareness. *Journal Pharm Market Management, 17*(1), 51-76.

Reuters, (2010, September 21). *Abbott Laboratories plans to cut 3000 jobs.* Opgeroepen op July 10, 2014, van The New York Times: http://www.nytimes.com/2010/09/22/business/global/22abbott.html

Rijksdienst voor Ondernemend Nederland. (2014). *Horizon 2020*. Opgeroepen op April 22, 2014, van Rijksdienst voor Ondernemend Nederland: https://www.rvo.nl/subsidies-regelingen/horizon-2020-onderzoek-en-innovatie?wssl=1

Rijksdienst voor Ondernemend Nederland. (2014). *Open Disruptive Innovation (ODI) & the SME instrument: Frequently Asked Questions 1.* Rijksdienst voor Ondernemend Nederland, Subsidies en financiering.

Roger, C. (2014). *The Pharma Licensing Negotiation Master Class.* Opgeroepen op July 1st, 2014, van C.E.L. for pharma: http://www.celforpharma.com/pharma-management/training/pharma-licensing-negotiation-course.html

D. D. Rohde, (2000). The orphan drug act: an engine of innovation? At wat cost? *Food drug law journal, 55*, 125-143.

D. Roland, (2014, June 02). *AstraZeneca seeking to get cancer drugs to patients early.* Opgeroepen op June 24, 2014, van The Telegraph: http://www.telegraph.co.uk/finance/newsbysector/pharmaceuticalsandchemicals/10870706/AstraZeneca-seeking-to-get-cancer-drugs-to-patients-early.html

P. Saviottti, (1998). On the dynamics of appropriability, of tacit and codified knowledge. *Research Policy, 29*, 843-856.

M. A. Schilling, (2009). *Strategic management of technological innovation.* New York: McGraw-Hill Education.

K. Schulman, S.Tunis, (2010). A policy approach to the development of molecular diagnostic tests. *Nat Biotechnology*, Vol 28; p1157-9.

U. Sekaran, R. Bougie, (2010). Non-response and non-response error. In U. Sekaran, & R. Bougie, *Research methods for business: A skill building approach* (p. 468). John Wiley & Sons.

J. Seman, (2003, March). In search of preferred status. *Pharmaceutical executive succesful product management supplement.*

S.Shiloh et al., (2002). Individual differences in rational and intuitive differences in rational and intuitieve thinking styles as predictors of heuristic responses and framing effects. *Personality and Individual differences*(32), 415-429.

B.Simonin, (1999). Ambiquity and the process of knowledge transfer in strategic alliances. *Strategic Management Journal, 20*, 595-623.

B. Smith, (2012). Excellence in market access strategy: A research-based definition and diagnostic tool. *Journal of Medical Marketing, 12*(4), 259-266.

G. Szulanskim, (1996). Exploring internal stickiness: Impediments to the transfer of best practice within the firm. *Strategic Management Journal, 17*, 27-43.

The Build Network Staff, (2013, December 24). *How to Create the Perfect Checklist*. Opgeroepen op August 20, 2014, van Inc.: http://www.inc.com/the-build-network/the-key-to-success-a-checklist.html

The Decision Group, (2011). *Dutch Life Sciences Outlook 2011.* Opgeroepen op July 2014, van Dutch Life Sciences & Health Outlook: http://www.thedecisiongroup.nl/wp-content/uploads/2012/01/Life-Sciences-Outlook-2011.pdf

The Decision Group, (2012). *Dutch Life Sciences Outlook 2012.* Opgeroepen op July 2014, van Dutch Life Sciences & Health Outlook: http://www.thedecisiongroup.nl/wp-content/uploads/2012/02/Life-Sciences-Outlook-2012-online-published-version.pdf

The Decision Group, (2013). *Dutch Life Sciences & Health Outlook 2013.* Opgeroepen op July 2014, van Dutch Life Sciences & Health Outlook: http://www.thedecisiongroup.nl/wp-content/uploads/2013/02/Dutch-Life-Sciences-Health-Outlook-2013_online.pdf

The Decision Group, (2014). *Dutch Life Sciences & Health Outlook 2014.* Opgeroepen op July 10, 2014, van Dutch Life Sciences & Health: http://www.thedecisiongroup.nl/wp-content/uploads/2014/02/DutchLifeSciencesOutlook2014.pdf

The Witherspoon Council on Ethics and the Integrity of Science, (2012, Winter). Appendix E: Overview of International Human Embryonic Stem Cell Laws. *The New Atlantis*(34), 129-146.

TI Pharma, (2014, June 21). *TI Pharma*. Opgeroepen op June 21, 2014, van TI Pharma: http://www.tipharma.com/

Topsectoren.nl, (2014, April 16th). *Ambities*. Opgehaald van Topsectoren.nl: http://topsectoren.nl/life-sciences-health/ambities

Total Orphan drugs, (2014, June 18). *AstraZeneca eyes early access schemes for cancer drugs.* Opgeroepen op June 24, 2014, van Total Orphan drugs: http://www.orphan-drugs.org/2014/06/18/astrazeneca-eyes-early-access-schemes-for-cancer-drugs/#sthash.DzSm1kps.dpbs

W. Tsai, (2001). Knowlegde transfer in intraorganizational networks: Effects of network position and absorptive capacity on business unit innovation and performance. *Academy of Management Journal, 44*, 996-1004.

M. Van Geenhuizen, P. Nijkamp, (2012). Knowledge virtualization and local connectedness among young globalized high-tech companies. *Technological Forecasting & Social Change*(79), 1179-1191.

I.Verniers et al., (2011). The global entry of new pharmaceuticals: a joint investigation of launch window and price. *Intern. journal of research in marketing*(28), 295-308.

S.Zahra, G. George, (2002). Absorptive capacity: A review, reconceptualization, and extension. *Academy of Management Review, 27*, 185-203.

L. A. Zucker, (1998). Intellectual human captial and the birth of U.S. biotechnology enterprises. . *American Economic Review, 88*, 290-306.