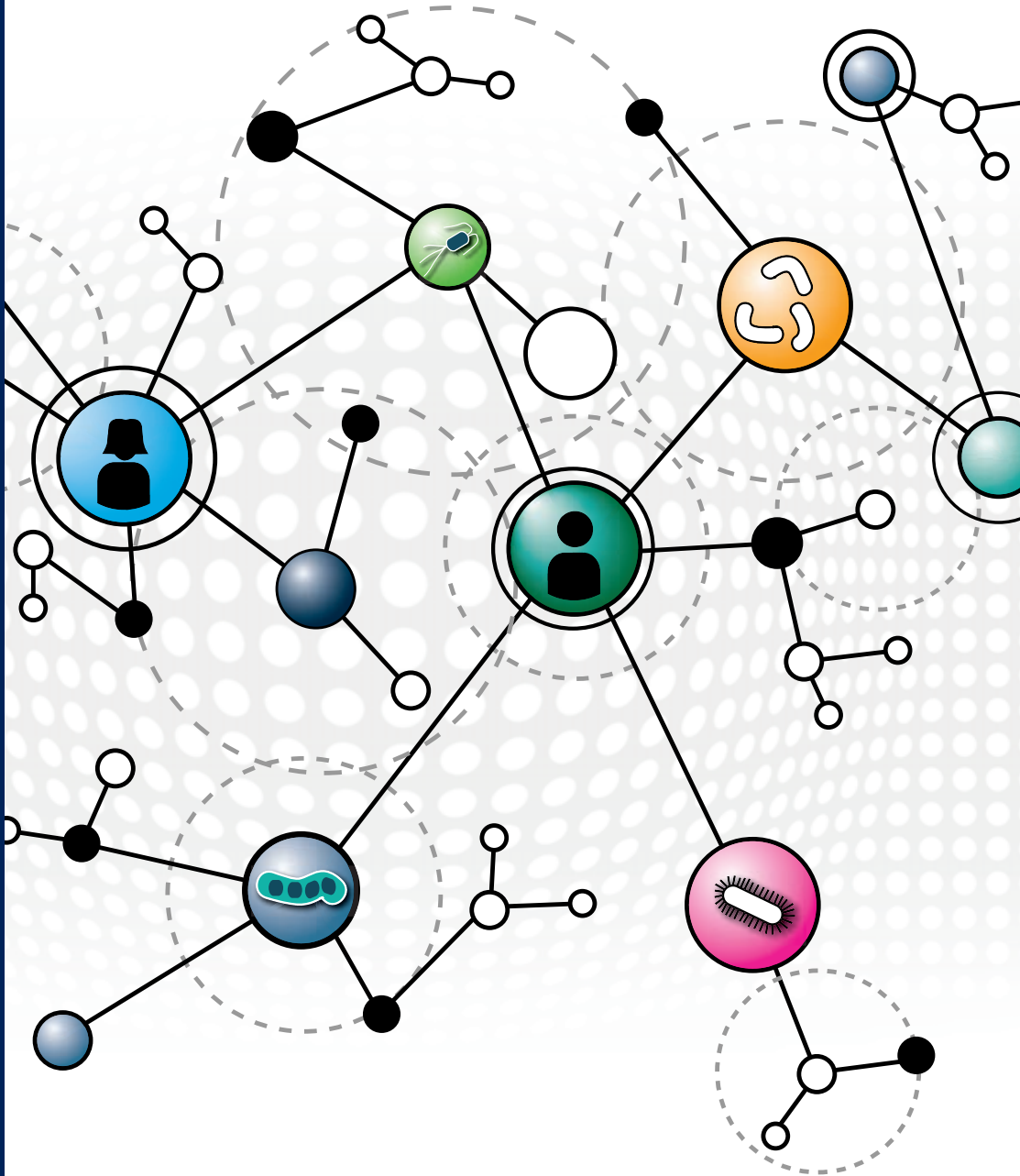ESTHER SOPHIA PRONKER

Innovation Paradox in Vaccine Target Selection

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Innovatieparadox in de selectie van infectieziekten
voor de ontwikkeling van vaccins

THESIS

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Esther Sophia Pronker

born in Nieuwegein

ERASMUS UNIVERSITEIT ROTTERDAM

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Chapter One: Introduction

1.1 Health and Wealth

Good health is an internationally recognized fundamental human right [1]. Health is also an important economic engine [2]. As published in Bloom's *Health and Wealth of Nations*, the positive correlation between a nation's wealth and an individual's health status is best described as mutually reinforcing [3]. Among the multiple challenges facing public health, infectious diseases are the second largest cause for mortality (Glossary 1.3.1).

"*Great pandemics and local epidemics alike have influenced the course of wars, determined the fates of nations and empires, and affected the progress of civilization, making infections compelling actors in the drama of human history.*"

Fauci and Morens (2012)[4]

To date, prophylactic vaccines are considered the most effective/cost-effective strategy for mitigating the spread of infectious diseases, thereby maintaining public health (Glossary 1.3.2 and 1.3.3) [5]. In fact, the history of population mortality statistics reveals that a combination of improved sanitary conditions, access to potable water, antibiotics, antivirals and vaccines has lead to a greater control over infectious diseases [6]. Vaccines have served the late-twentieth century population by eradicating smallpox, and significantly reducing the global incidence of various other infections, including; poliomyelitis, diphtheria, tetanus, pertussis, measles, mumps, rubella, *heamophilus influenza* type B, hepatitis A virus, hepatitis B virus and pneumococcal bacteria [6]. Additionally in the veterinary field, appropriately directed vaccination campaigns against the rinderpest virus have lead to its eradication in 2011 [7, 8].

This incredible accomplishment has been enabled due to improvements in the accessibility of vaccines. Improving access to essential medicines is more than just a simple logistical equation between the supplier and customer. Access involves pharmaceutical, social, political and economic interests, essentially encompassing four key processes; architecture, availability, affordability and adoption [9-11]. Here we will not discuss architecture and adoption.

Starting with *affordability*: global vaccine coverage rates have been stimulated by various sustainable financing mechanisms. Such procedures mediate the financial aspects between the customer- (vaccine acquisition budgets of local governments) and the supplier-side (vaccine price as set by the manufacturer). These economic tools include the extended programme of immunization (EPI) and a tiered-pricing scheme [12-15]. EPI is a programme set up by the World Health Organization (WHO) in 1974 in order to ensure that children all over the world have access to vaccines [16]. Tiered pricing allows for the average price per vaccine unit to be adjusted according to a nation's income level [17, 18]. Both systems have been realized through collaboration between numerous public and private stakeholders, including; the WHO, United Nations Children's Fund, Pan-American Health Organization, Global Alliance for Vaccines and Immunization, the Bill and Melinda Gates Foundation, the Vaccine Fund and various other (non-) governmental institutions [13, 16].

In terms of *availability*: although vaccine development was initially undertaken by governmental public-sector institutions, vaccine development today is dominated by private-sector commercial ventures [19, 20]. The vaccine industry is currently led by five biopharmaceutical manufacturers, holding a combined market share of 85%[A]. Considerable advancements regarding (fundamental) knowledge on epidemiology, the immune system and vaccine and antiviral technologies drive innovation. As a result, the industry has successfully marketed paediatric and adult prophylactic vaccines covering over 25 infectious diseases [21]. Moreover, the application of vaccines is expanding to include immunotherapeutic targets for both cancer and chronic auto-immune diseases [22, 23].

In order to commercialize a vaccine, the candidate antigen has to complete the pharmaceutical value chain (PVC). The value chain describes the (inter)nationally regulated chronological stages an antigen candidate has to complete - starting from the discovery phase through to human clinical trials - before it can be commercially exploited on the market (Glossary 1.3.4) [24]. As a candidate molecule successfully proceeds along the PVC phases, its value - as expressed in financial terms - increases. This process of value accumulation is also referred to as valorization (Glossary 1.3.5), and occurs mainly due to two reasons. First, the amount of resources required for developing the candidate molecule accumulates progressively with each consecutive phase. Second, with each successfully completed development phase the probability of regulatory approval for market entry rises. In other words; risk reduction of the financial investment is correlated with a higher value[25].

Nevertheless, vaccine development is threatened by the so-called innovation paradox. In short; regardless of increasing R&D activities, the predicted output - as measured by successful market entry of the product - is lacking [26]. This situation has intensified over the past few decades and significantly affects the productivity of vaccine candidate valorization. Reasons include, but are not limited to; rising R&D costs, lower approval rates, vaccines competing with enhanced best standards of care, static patent timelines in combination with longer development timelines, an increasingly demanding regulatory environment and more stringent pricing and reimbursement criteria [27-29].

Additionally, public health is continually challenged by re-emerging and newly emerging infections as well as pathogen resistance to available intervention strategies, including anti-infectives and vaccines. Consequently, the persistent threat of the unmet medical need, want or demand challenges vaccine developers to anticipate future epidemiological outbreaks [6] (Glossary 1.3.6). Furthermore, in the view that certain infectious diseases are known as poverty-inducers, it is critical to select the appropriate target disease area for vaccine development [30]. Only through continued innovation will the biopharmaceutical community be able to respond appropriately to the substantial burden of the infectious pathogen. An appropriate response combines a timely production of a safe and effective high quality vaccine, while ensuring wide-spread access for the (high risk[B]) population groups.

[A] The so-called 'big-five' consist of: Sanofi Aventis, GlaxoSmithKline, Merck, Pfizer and Novartis

[B] High risk groups include children, elderly, and immunocompromised patients

Here we evaluate the impact of the innovation paradox on selecting human infectious disease targets for vaccine development. Due to the complex nature of the topic, it is approached using a multidisciplinary perspective, combining a wide-range of scientific disciplines including epidemiology, virology, bacteriology, immunology, economics, management and organization. Moreover, the research as presented in this dissertation focuses on the innovation paradox from the individual- and organizational-levels (Figure 1.1). In essence, it is at these two levels that vaccine development takes place and where target infectious disease selection has direct consequences to the unmet medical wants, needs and demands at the societal-level. The aim is to keep vaccine valorization innovative and productive, for the benefit of public health.

Figure 1.1   Defining Multi-level Analysis

This dissertation focuses specifically on the individual-/ micro-level and organizational level regarding the innovation paradox in vaccine target selection.
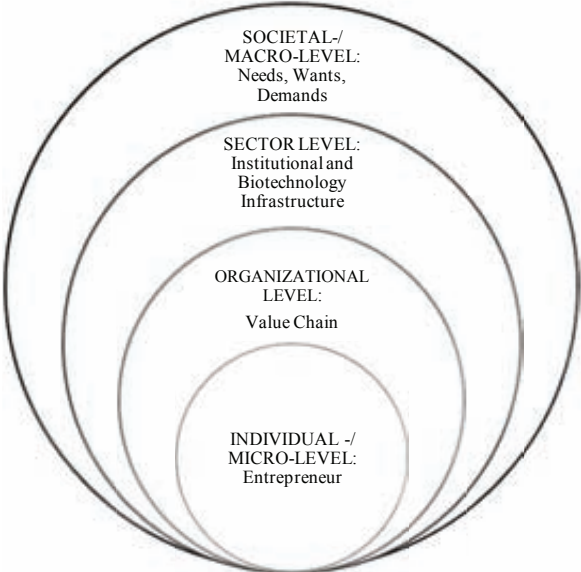
1.2   Outline

The studies presented in this dissertation are organized according to the framework in Figure 1.2. The first section is a general introduction to entrepreneurial-/micro-level concepts of vaccine development. The second section concentrates on the organizational-level productivity and dynamics. Section three reflects on all previous chapters, evaluating the impact of the organizational environment on entrepreneurial activity. The dissertation ends with a discussion, presenting the lessons learned regarding the effect of the innovation paradox on the valorization cycle, which in turn influences vaccine target selection.

Chapter 2 introduces entrepreneurial level concepts, focusing on the specific roles of scientists, inventors and entrepreneurs, and their contribution to the field of vaccine development. Although the chapter focuses on vaccine development, the average probability of success and milestone investment per phase is contrasted with that of drug development. Ultimately we attempt to answer the question; which entrepreneurial role would be most effective in order to advance, promote, and commercialize prophylactic treatments against infectious diseases? Through applying entrepreneurial theories on science-based venturing, the innovative capacities of the various entrepreneurial roles contributing to the value chain are evaluated.

Chapters 3 and *4* define markers of organizational-level productivity for vaccine development. *Chapter 3* reviews the gold pharmaceutical industry standards for the success rates and associated costs of new chemical entity (NCE) development. Although a publication by Dimasi (2003) is widely quoted as the gold standard for describing the industries' productivity, the literature survey resulted in an additional six publications on the same topic. We also introduce the link between productivity and risk profiles, and analyze the various calculating procedures with which to determine the productivity rate.

Chapter 4 fine-tunes the calculation parameters and risk profiles for human vaccines in development. A risk profile combines phase duration with market entry probabilities, and is granulated based on target disease area. Furthermore, risk profile behaviour for chronic versus acute infectious diseases, and prophylactic or therapeutic vaccines is investigated. Ultimately we demonstrate that risk profiles are useful tools in calculating the productivity of the vaccine industry, and delineating the productivity gap.

Both *Chapter 5* and *6* focus on organizational-level dynamics, evaluating the factors directly influencing the development timelines of the vaccine value chain. *Chapter 5* evaluates the productivity of the administrative paper trail of a clinical phase I trial in an academic research organization (ARO). The focus lies on sponsor queries. Sponsor queries are officially recorded questions concerning potential discrepancies between the raw paper data and its' electronic, manually entered copy. Current protocols require a 100% check of all data points using various mechanisms. Such quality checks are completed by ARO and the clinical trial sponsor as well as regular governmental and international audits. This study explores the error-rate of data management quality control mechanisms and delineates a novel quantitative approach for evaluating the productivity of clinical trial data management procedures.

Chapter 6 offers an exploratory view on the potentially rate-limiting factors encountered during adjuvanted-vaccine development that affect value chain dynamics. Adjuvants are considered immunostimulating substances that can be added to a vaccine. Although adjuvants have the potential to elicit adverse reactions, they also offer certain benefits including; increasing the immune response in senescent population groups and dose-sparing properties. Nevertheless, after approximately 90 years of R&D, we question why only four adjuvants have been approved for use in human vaccines? Although ample literature is available describing the main risks for developing adjuvanted-vaccine candidates, it remains unclear as to how these potentially rate-limiting factors compare and

interact. Key opinion leaders in the field of adjuvanted-vaccine development were approached in order to collect a unique qualitative empirical dataset.

Chapter 7 reflects on the previous studies from an entrepreneurial-perspective. This chapter essentially reviews key ingredients learned from organizational-level productivity and dynamics, which have the potential to greatly enhance entrepreneurial activity.

Figure 1.2   Organization of the research chapters
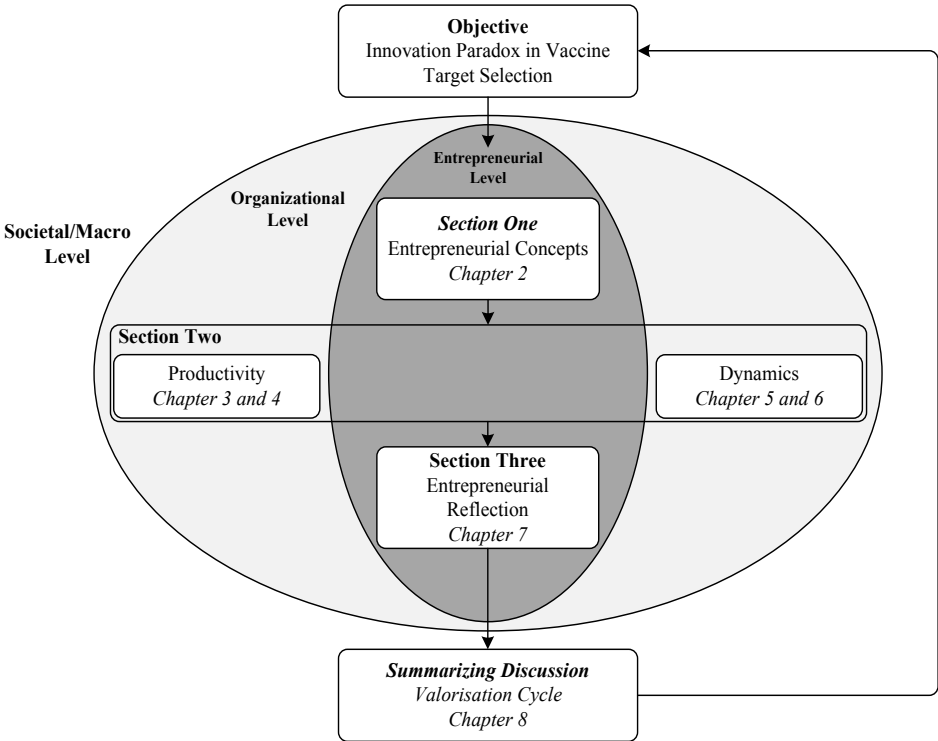
1.3 Glossary of Central Concepts

1.3.1 *Epidemiology*

Epidemiology is the study of the incidence, distribution/spread and control of diseases [31]. When it comes to studying infections; communicable pathogens remain a leading major cause of mortality, disability and social and economic disorder, disproportionally affecting developing countries [32]. Infectious diseases account for approximately a quarter of annual deaths worldwide (Figure 1.3). The majority of these 15 million live in low- to middle-income countries [33-35].

Figure 1.3   Global estimated annual causes of mortality [33]
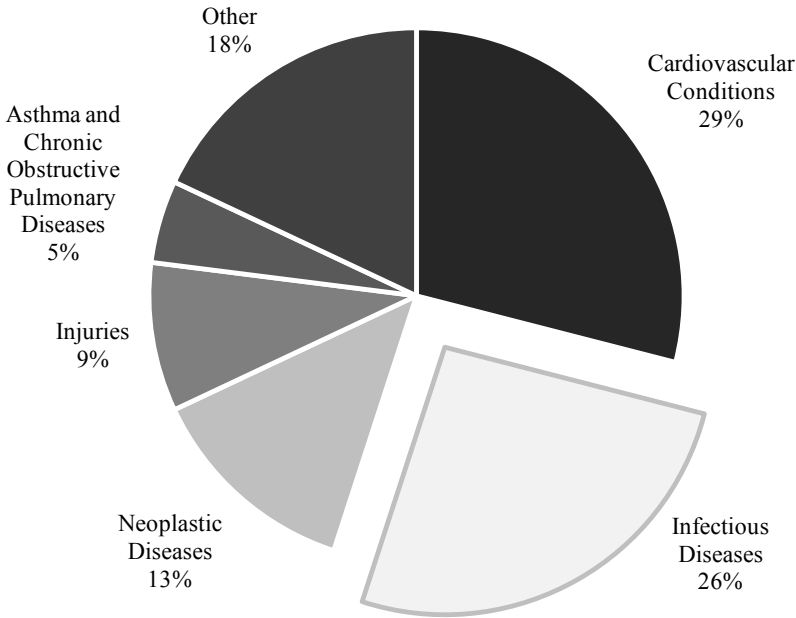
The most common infectious diseases affecting the human population include respiratory infections, HIV/AIDS, diarrhoeal diseases, tuberculosis and malaria (Table 1.1) [33]. If these statistics were to take disease latency into consideration, the number of individuals affected would be far more substantial. For example; over 31 million people are infected with HIV [36], at least 350 million individuals are carriers of Hepatitis B, and another 100 million for Hepatitis C [37]. Although vaccines are considered the best approach for all of the pathogens listed in Table 1, there are still multiple unmet medical needs (Glossary 1.3.6).

One of the key features that distinguishes infectious diseases from other human diseases is the theoretical notion that infectious diseases can be eradicated [4]. Eradication is defined as

"Permanent reduction of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts, whereby intervention measures are no longer needed [38]." Even though global eradication programmes find significant financial, political and societal support[39], they are considered a high risk, lengthy and resource intensive process. The availability of a vaccine is simply not sufficient. Other features should also be into account, including but not limited to; the biological features inherent to the pathogen and its replication life-cycle, technological factors, cost-benefit analysis of resources required, and surveillance infrastructures [38]. Infectious disease candidates eligible for eradication in the near future - as identified by the Carter Centre International Task Force - includes poliomyelitis [40-42].

Table 1.1   Global estimated annual mortality rates for infectious diseases, and availability of prophylactic vaccines [6].

Infectious Disease	Mortality Rate/ Millions [33]	Example	Vaccine Availability
Respiratory Infections	3,96	Seasonal Influenza	Yes; inc. adjuvanted vaccines
HIV/AIDS	2,77	HIV/AIDS	No
Diarrhoeal Diseases	1,80	Rotavirus	Yes
		Enterotoxigenic Escherichia coli (ETEC)	No
Tuberculosis	1,56	Tuberculosis (TBC)	Yes; limited long-term protection
Malaria	1,27	Malaria	No
(Preventable) Childhood Diseases	1,12	Heamophilus Influenzae Type B	Yes
		Respiratory Syncytial Virus	No; monoclonal antibody
Sexually Transmitted Diseases	0,18	Human Papilloma Virus	Yes
Meningitidis	0,17	Meningococcal Meningitidis	Yes; not all strains
Hepatitis B and C	0,16	Hepatitis B Virus (HBV)	Yes
		Hepatitis C Virus (HCV)	No
Tropical Parasitic Diseases; other than Malaria	0,13	Leishmaniasis	No
Dengue	0,02	Dengue	No
Other; Newly emerging Infections	1,76	Japanese Encephalitis virus	Yes
		Enterovirus 71 (EV71)	No
		Anthrax Bioterrorism	Yes; US military only

1.3.2   The Immune System and Vaccines

The immune system is a complex bodily process that - under normal circumstances and in healthy state - actively eliminates infectious pathogens. An immune response is a coordinated event between innate and adaptive components of the immune system. This response aims to neutralize and clear the pathogen as efficiently as possible while attaining some form of immunological memory in case of future contact. Immunological memory can only be established through the adaptive immune system, which consists of two arms; the cell-mediated immunity and humoral antibody mediated immunity [43].

Nevertheless, infectious pathogens are continuously evolving, persistently posing a threat to an individual's health status. This evolutionary rate of change is driven by a combination of mutations in genetic material and natural selection processes [44]. Such changes allow for the pathogen to adapt in order to infect other immunologically naïve species (Zoonosis is an example), and/or evade the host's immune system [45]. This evolutionary rate is also dependent on the antigenic variability of the pathogen. An example of a pathogen with low antigenic variability is the measles virus; one infection episode with the wild-type virus often leads to life-long immunological memory [46, 47]. Examples of pathogens with higher antigenic variability include influenza virus (variability is seasonal) and HIV/AIDS (variability can be daily) [45].

In the situation where the pathogen is highly infectious, has a high mutation rate, or if the immune system cannot perform optimally (e.g. in the very young, the elderly or immunocompromised patients), or a combination of all conditions: the infection can result in complications with sometimes fatal consequences. It is under these circumstances that the immune system can benefit from either passive or active immunization through administration of vaccines, antivirals and/or isolated immunoglobulins [43].

Historians believe the origins of vaccinology most likely stems from the homeopathic beliefs that: "a small dose of an infectious disease could protect against severe disease [19]." Even as early as the 11th century Chinese documents describe immunization techniques against the smallpox virus: administering dried smallpox scabs from an infected individual to the naïve recipient via the skin or the nasal route [19, 48]. It is believed this technique became available to the British in the early 18th century, from where the procedure spread to other parts of Europe and America [48]. Nevertheless, popular biology books have adopted Edward Jenner's Cowpox experiments in the 1790s as the initiator of the vaccinology discipline. Ultimately his research on the pox virus proves a vital cornerstone towards the global eradication of smallpox in 1977 [6, 20, 49]. Consequently, from the late 18th/early 19th century onwards; vaccine developers started designing vaccines for a range of human infectious diseases [6, 20].

However, vaccination has its share of limitations, of which we present a few. First, virtually all successful vaccines used today are based on the induction of an adequate humoral immune response. Examples include paediatric Measles, Mumps and Rubella (MMR) and Diphtheria, Pertussis, Tetanus and Polio (DPTP) combination vaccines [6]. Stimulating the other protective cell-mediated arm of the immune system has proven to be more challenging. Nevertheless, for some infectious agents a humoral response is simply

not a sufficient correlate of protection [50, 51]. Second, there are limits to the immunogenicity of administering the antigen. Solutions are sought in the direction of improving epitope identification, administration routes, adjuvants [52-55] and delivery vehicles (including pre-loaded dendritic-cells, lipid carriers, and various viral-, plant- and bacterial-vectors) amongst others [56]. As a final point, vaccination is associated with certain health risks [57]. In some cases the adverse reactions (allegedly) caused by the vaccine, have resulted in the regulatory authorities removing that product from the market. Such a suspension can be permanent or temporary; in the latter case the product will be pending additional research. One recent example includes the temporary suspension (currently authorized again) H1N1 pandemic influenza vaccine Pandemrix ® by the European competent authority, on account of alleged association with increased incidence rate of narcolepsy[58]. Nevertheless, in the view that prophylactic vaccines are generally administered to healthy individuals, the statistical likelihood of developing a side-effect is kept to the absolute minimum.

1.3.3 Vaccine Cost-Effectiveness

Vaccines are considered to be the most cost-effective method in controlling the spread of communicable diseases [59]. On the other hand, therapies for infectious diseases are not exclusive to vaccine developers. Although this fact is not highlighted within the dissertation, it is important to consider nonetheless; vaccines are in competition with NCE when it comes to developing therapies targeting infectious diseases. Examples of such diseases include HIV/AIDS and Malaria, for which therapies are designed by altruistic foundations, pharmaceutical companies and biotechnology firms.

Vaccines are available in three varieties; prophylactic (prior to the infection), therapeutic (during disease manifestation), or post-exposure prophylactic (PEP). PEP is also known as secondary prophylaxis, whereby the vaccine is generally administered within a few hours after exposure to the pathogen. As elaborated in *Chapter* 4, the majority of available vaccines targeting infectious diseases are prophylactic. A smaller portion of available vaccines are therapeutic, and most often target cancer and auto-immune diseases. Therapeutic vaccines for the treatment of HIV/AIDS and Hepatitis C Virus (HCV) are currently in the development pipeline. Only a sub-section of available vaccines are considered PEP, and target diseases such as rabies, tetanus and Hepatitis B Virus (HBV).

Nevertheless, vaccines are considered to provide more value for every invested dollar when compared to that same dollar invested in a new chemical entity [60-62]. One reason is the fact that NCE largely focus on therapeutic applications, whereas vaccines are mostly prophylactic [63]. Additionally, vaccines require a lower average investment and shorter development timelines when compared to the average drug in development (*Chapter 2*).

1.3.4 Pharmaceutical Value Chain

The value chain is also referred to as the *theory on safety and efficacy*. Each development phase focuses on exploring and establishing safety and efficacy of the candidate entity[A] while maintaining specific qualitative and ethical standards [64, 65]. It has evolved into its current format to reflect this theory, given specific fraudulent cases and medical disasters[66,67]. Such incidents have resulted in rethinking the ethics and procedures for human clinical trials, contributing to the establishment of the following; the Nuremburg Code in 1947 [68, 69], the World Medical Association Declaration of Helsinki in 1964 [70] and International Conference of Harmonization (ICH) Good Clinical Practice in 1996 [71].

The value chain starts off with the discovery phase. The target disease is selected, and the screening of potential candidate entity begins. In this selection process, hundreds of candidates are selected from thousands of entities based on preliminary efficacy data. *In silico* and *in vitro* methods dominate this stage, often resulting in a patent application.

Following is the pre-clinical phase where the candidate entity is tested using *in vivo* animal models. In this phase, data on the efficacy and toxicity of the candidate is collected, to identify its potential for treatment in humans.

Between animal testing and human clinical trials, the clinical trial sponsor compiles a dossier on the safety and efficacy data of the candidate entity. This file is submitted to the appropriate regulatory authority and ethical review board for assessment. The dossier has to be approved before advancement to the next PVC stage (Table 1.2).

Table 1.2   Submitted documents required for the candidate molecule to advance from pre-clinical to human clinical trials, per region [71, 72].

Region	Regulatory Agency	Document Title
United States (US)	Food and Drug Administration (FDA)	Investigational New Drug (IND)
Europe (EU)	European Medicines Agency (EMA)	Clinical Trial Agreement (CTA)
Japan	The Ministry of Health, Labour and Welfare – Pharmaceuticals and Medical Devices Agency	Clinical Trial Notification (CTN)
Brazil	Brazilian Health Ministry – Brazilian Health Surveillance Agency	Comunicado Especial (Special Communication)
Russia	Ministry of Health and Social Development	IND
India	Ministry of Health and Family Welfare - Central Drugs Standard Control Organization	(Clinical Phase I trials not allowed)
China	State Food and Drug Administration	Clinical Trial Application or Chinese IND

[A] Candidate entity in this description can be either a NCE or a vaccine antigen.

Clinical development is defined as; "research using human volunteers (also called participants) that is intended to add to medical knowledge [73]". A randomized, double-blind, (placebo) controlled human trial is the undisputed instrument for proving a candidate entity's safety and efficacy, and consists of four sub-phases (Table 1.3).

Table 1.3   Sub-phases of clinical development phase [73]

Pk/PD	Pharmacokinetic/ Pharmacodynamic properties
ADMET	Acronym for drug administration, delivery, metabolism and excretion pathways and toxicology study

Clinical sub-phase	Aim	Purpose	Quantity Volunteers	Average Length
Phase I	Exploratory	First in human safety; Multiple dose; Pk/Pd and ADMET	Healthy; 20-100	Several months
Phase II a	Exploratory	Short-term safety; Dose tolerability; Proof of concept	Patients; Several 100	Up to 2 years
Phase II b	Confirming	Effectiveness of dose regimen; Drug delivery; Biological activity	Patients; Several 100	Up to 2 years
Phase III	Confirming	Safety; Dosage; Effectiveness; (often) Multi-centre	Patients; +/- 1000	1 to 4 years
Phase IV	Post-Marketing	Observational short-term and long-term side-effects	Patients	After market entry

Prior to market entry and Clinical Phase IV, the sponsor submits another report to the regulatory authorities, for example the Common Technical Document (CTD) or the ASEAN[A] CTD [72]. The CTD is an initiative by the ICH, and aims at unifying the interpretations of the rules and regulations for medical drug and device development at a global level. This dossier describes the experimental results of the candidate entity, given superiority or non-inferiority for certain safety and efficacy parameters. Regulators examine the evidence, and decide whether the candidate meets all safety, efficacy and quality standards to allow market entry. Even after approval the entity is subjected to testing in the form of a phase IV post-marketing surveillance clinical trials. In this phase the short- and long-term side effects of the product in patients are monitored. This phase can last as long as the market life-cycle of the entity.

[A] ASEAN – Association of South-East Asian Nations

1.3.5 Valorization, Innovation, Productivity Gap and Innovation Paradox

The concepts of valorization and innovation, as well as the productivity gap and the innovation paradox, are closely related and deserve further clarification in order to avoid confusion (Figure 1.4).

In the case of vaccine development, both valorization and innovation pathways are laid-out by the pharmaceutical value chain. Valorization describes the processes of allocating a value toward an entity, and creating added value for its financial asset [74]. This entity could take any shape or form, including but not limited to; product, process, service, technology and knowledge. The goal of valorization is to realize an added value for the transaction, as the entity is transferred from one development step to the next. Over the course of the value chain, valorization is the accumulation of value over the successfully completed phases. It is distinct from technology transfer processes, which (only) supervises the exchange of the entity between development phases.

Innovation can also be viewed as adding value, whereby the end-result is a commercial entity [75]. In this case, the new entity is essentially known as the invention, and the degree of novelty is assessed as either incremental or radical. Additionally, the value of an innovation is determined by market entry, for which the value is influenced by the dynamics of supply and demand [75]. Therefore, the value of innovation is in absolute terms, encompassing all value chain procedures.

The productivity gap describes the situation whereby the resources invested in the R&D process do not correlate with the anticipated output [76, 77]. In the case of vaccine development, R&D procedures are synonymous to the various phases of the pharmaceutical value chain, and the output is a measure of successful market authorized vaccine products.

The innovation paradox describes the situation whereby the number of novel entities/inventions do not correspond to the anticipated commercial market entries [78]. This concept is separate from the knowledge paradox, which defines the complex relationship between the sharing of invention and the necessities for its protection through intellectual property strategies [79].

Figure 1.4   Valorization, innovation and technology transfer placed in context of the vaccine value chain
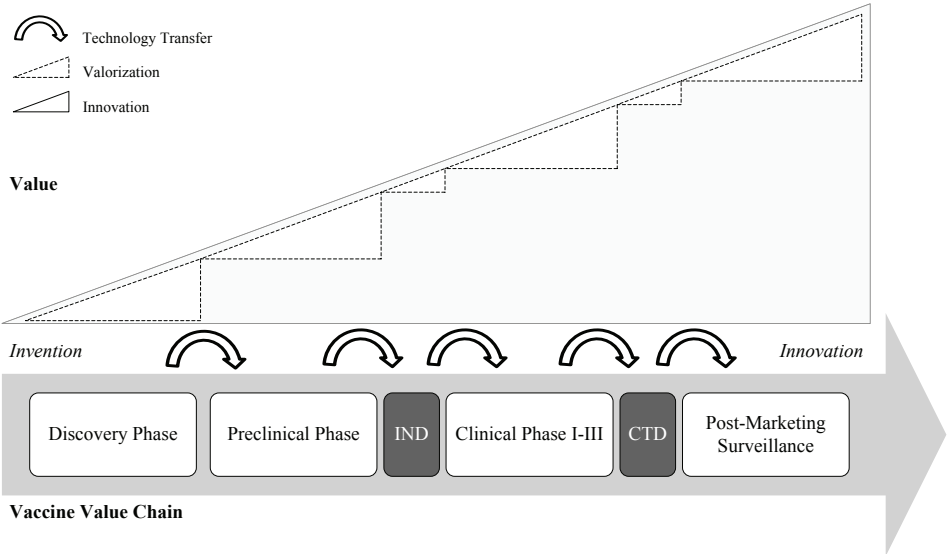
1.3.6   Unmet Needs, Wants and Demands

When describing the innovation paradox in vaccine target selection, it is important to understand the differences between the (un-) met medical need, want and demand. In the view that these terms often imply different connotations for the various scientific disciplines, they deserve further clarification.

A need describes the fundamentals required to sustain a healthy individual. This term is generally used by medical practitioners and health care agencies [80]. The medical need is also defined as: "the quantity of medical services which - according to expert medical opinion and as permitted by existing medical knowledge - is to be consumed over a relevant period of time in order for the individual to remain or become 'healthy' [80]."

A want is defined as a desire, also known as pleasure seeking that drives consumption patterns [81]. It is: "the quantity of medical services which it's members feel they ought to consume over a relevant period of time based on their own psychic perceptions of health needs [80]."

Demand is defined as: "a multivariate functional relationship between the quantities of medical services that it's members desire to consume over a relevant time period given the levels of price of goods and services, financial resources size and psychological wants of the population as reflected by consumer tastes and preferences for (all) goods and services[80]."

Chapter Two: Entrepreneurship and Science-Based Venturing

The Case of Vaccine Development

Abstract

Through applying entrepreneurial theories on science-based venturing, the innovative capacities of the various entrepreneurial roles contributing to the value chain are evaluated. *Chapter 2* introduces entrepreneurial level concepts, focusing on the specific roles of scientists, inventors and entrepreneurs, and their contribution to the field of vaccine development. Entrepreneurial theories are elaborated on, and applied to Fritz Hoffman-La Roche and Louis Pasteur. Although the chapter focuses on vaccine development, the average probability of success and milestone investment per phase is contrasted with that of drug development. Ultimately we attempt to answer the question; which entrepreneurial role would be most effective in order to advance, promote, and commercialize prophylactic treatments against infectious diseases?

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2.1 Introduction

A major challenge in every science- and technology-driven industry is the continuous development of novel products, concepts, and designs based on new scientific achievements. It requires a bridging of the gap between the organizations that conduct fundamental and applied research (universities, academic hospitals, research institutes, and industrial research departments) and those that develop them (existing and newly created companies). Apart from the generation of new knowledge and its effective transfer to business and society (i.e., commercializing scientific discoveries), science-based venturing includes distinctive roles that have to be taken by scientists, entrepreneurs, and small and large businesses.

This chapter addresses the phenomenon of science-based venturing in a biomedical field. It outlines the academic and business context that shapes research on viral infectious diseases and the development of vaccines and the strategic interaction between universities, small and young firms, and established companies. Fuelled by a series of scientific breakthroughs in the second half of the 20th century, the life-sciences sector has rapidly expanded and has successfully developed itself into an engine of economic growth. Moreover, considering technology push (new scientific breakthroughs, e.g., from stem cell research), market pull (aging population, quality of life) and business need (new products to sustain and boost turnover in the pharmaceutical and biotechnology industries), the life-sciences sector promises to develop even further in the decades ahead of us.

The societal and economic value of research, development, and the diffusion of preventive vaccines goes beyond measurement, and the effective application of immunization strategies cannot be ignored. In the words of Andre (2001): "It is undeniable that the use of vaccines has prevented more premature deaths, permanent disability and suffering, in all regions of the world, than any other medical discovery or intervention [59]." Immunization strategies are considered highly effective in targeting a plethora of external pathogens and also having the potential to prevent or even cure chronic infections, allergic conditions, autoimmune diseases, and cancer [82]. The effectiveness of this intervention can be attributed to the fact that it employs the host's own immune system to attain protection. This feature is inherent to the technology and distinguishes vaccines from other pharmaceutical products. Among the various techniques available for immunization, active vaccination is the most common. Given their impact on public health, vaccines form an inevitable part of our future. Currently, more than 900 international vaccine projects are underway internationally, each requiring an investment in the order of U.S. $200 to U.S. $900 million. It has been estimated that each vaccine development project takes about 10 years to complete from preclinical phase to approval, and no more than 22% will attain market approval [83].

This chapter aims to explore the different roles scientists, entrepreneurs, and managers of small and large firms play in advancing the health and life sciences, and apply this with a special focus on vaccine development. We provide a general description of the academic and business context to illustrate the holistic and complex nature of drug development, as well as the distinctive roles that scientists, entrepreneurs, and small and large firms play in the chain of activities from discovery to market. The chapter is divided into two main

sections. It begins with a theoretical explanation of science-based venturing and knowledge transfer, including historical accounts of Louis Pasteur and Fritz Hoffmann, to delineate the division between the roles of inventor and entrepreneur. It then zooms in on the captivating world of the vaccine research and development value chain and concludes by defining the current state of vaccine development and the actors and issues that influence it.

2.2 Science-based Venturing: Entrepreneurship, knowledge transfer and innovation

The three building blocks of science-based venturing are invention, knowledge transfer, and entrepreneurship. In this section we will focus on the different roles that can be distinguished in bringing new ideas to the market: the role of researchers, the role of liaison officers and other transfer professionals, and the contribution of entrepreneurs and their small or large firms. Starting with the profiles of academic inventors, Stokes (1997) came up with a clear and useful 2 x 2 matrix through which he mapped the efforts of scientists. This included they type of research they do (i.e., basic research, more applied R&D, or both) and the extent to which scientists take the interests of users, sponsors, and other stakeholders (us) into account while carrying out their research (from no involvement to user-inspired basic research to pure applied research) [84]. By mapping the scientists' considerations of us (yes/no) and the quest for fundamental basic research understanding (yes/no), Stokes generated four quadrants: from basic research that is performed without any thought being given to practical ends (an example is the physicist Niels Bohr), to user-oriented basic research capturing the benefits from new scientific knowledge and applying them effectively (a clear case of this is Louis Pasteur), to pure applied research that hops from one experimental project to another (Thomas Edison). The 2 x 2 matrix is completed by the 'bird-watching' quadrant in which no real question for fundamental understanding is present and where a (potential) consideration of use is absent, that is, watching birds just for the fun of it. Basic research is directed toward a more complete understanding of nature; it embarks upon the unknown, attempting to enlarge the realm of the possible. Applied research concerns itself with the elaboration and application of the 'known' and aims to convert the possible into the actual by systematically adapting research findings into useful materials, methods, and processes. Pasteur combined the extreme poles of the research spectrum by doing basic research and laboratory work in the domains of crystallography, biochemistry, and immunology with real-world utility potential (i.e., by developing preventive vaccines), but he never lost sight of the desire to advance scientific understanding [85].

For new knowledge to be effective and for the efforts of scientists and inventors to have an impact, the gap between knowledge generation and its application in the market place or society must be bridged. For that purpose, a working relationship between inventors and researchers on the one hand and entrepreneurs, established firms, and consumer (patient) groups on the other has to established. Knowledge transfer involves the development of an idea from a (public or private) laboratory into a commercial product, in this case involving the transfer of people, knowledge, knowhow, and practices from a university or research establishment to industry and society. The key mechanisms in technology transfer are

cooperative extension and outreach to business and society on one side and patenting, licensing, and spin-off creation on the other [86]. Whereas the former focuses on the development and dissemination of publicly available technologies (notably in the agricultural domain), the latter is aimed at making money from the inventions of public or corporate researchers through the sale of patents, licensing, and royalty payments, and equity in spin-off companies. In the former case, there is a strong belief in the free dissemination of knowledge, for instance, through publishing, consulting, and collaboration between university and industry scientists and the idea of appropriating and commercializing intellectual property is opposed. In the latter case, alternatively, private gains from academic research are sought and secrecy requirements to protect proprietary information are met; the university starts licensing its intellectual property rights (IPR) in exchange for cash, (future) sponsored research, or equity (i.e., taking shares in new ventures).

Smith and Miner (1983) developed a typology of entrepreneurs and their businesses on the basis of the motivations and the management styles of the business owners and the types of firm they establish and run. Initially, they identified the 'craftsman' and the 'opportunistic entrepreneur,' as well as the organizational vehicles with which they are associated and the respective rigid and adaptive firm structures [87]. The craftsman is characterized by limited education and training, low social awareness, difficulty interacting in the social environment, and a short-term perspective. The opportunistic entrepreneur is the polar opposite, having a broad education, high social involvement, the confidence in his or her ability to deal with the social environment, and an orientation toward the future. Smith and Miner (1983), together with Bracker (1992), later identified a third category, the inventor-entrepreneur, who focuses on obtaining patents and making new products. Whereas the craftsman is in the business of making a better product and the opportunistic entrepreneur is trying to build a better company, the inventor-entrepreneur lives to invent; his or her sole purpose in doing business is to discover new things, obtain patents, and generate new products [88].

Successful innovation requires a collective effort in bringing together people, ideas, and objects that were previously separate, and also when it comes to effective networking among heterogeneous ties spanning various markets and technologies. One successful strategy is combining what they already know and recombining existing ideas and practices from other industries and innovators [89]. Edison, for instance, owed his success not so much to his ability to build something out of nothing but rather to the way he managed to exploit his network, borrow the ideas of others, and incorporate and recombine them in his breakthrough innovations. Edison is an example of a technology broker, someone who links otherwise disconnected communities in an attempt to maximize their range of connections. By doing so, a technology broker is in a better position to be the first to see how people, ideas, and objects from one world may provide valuable solutions in another.

2.3   Vaccine Development in the 19th Century: The scientist and the entrepreneur

The emerging biomedical industry in the 19th century was shaped by scientists such as Louis Pasteur and entrepreneurs such as Fritz Hoffmann. Some of the smaller businesses turned themselves into large pharmaceutical companies (e.g., Hoffmann-La Roche) and created a value chain running from invention/discovery to actual testing and the usage of medical treatments.

2.3.1   *Louis Pasteur*

Whereas some scientists like Bohr, Darwin, and Einstein saw science and politics as rather separate spheres and never engaged much in combining their scientific and technological activities with education and/or selling it to the larger public, the microbiologist Pasteur saw science, politics, and technology as one tightly woven whole. He combined his dedication to science with aggressive self-promotion and a strong defence against critics, stating that his work had a real impact on society [85, 87]. Although Pasteur was involved in some commercial activities during his career (he did patent but did not establish a firm), he showed truly entrepreneurial behaviour though his fundraising activities and the fact that he addressed the needs of sick people, farmers, and the beer and wine industry directly. Furthermore, together with others, Pasteur established a new private research institution that carries his name.

In the early days of Pasteur's research career, his focus was on crystallizing chemical structures, a technique that subsequently proved to be of major importance in alcoholic fermentation and drug design processes. After having read about beverage contamination, his research moved away from crystals and shifted toward the role of microorganisms in fermentation, with special reference to wine and beer, before carrying out his well-known studies into infectious diseases in animals and humans (e.g., anthrax and rabies). His research was triggered by a curiosity to solve specific scientific puzzles concerning microbes or germs as agents of fermentation but also as agents of disease. He was also driven to articulate the needs and solve the problems of farmers, textile manufacturers, veterinarians, beer brewers, wine growers, doctors, and their patients.

At the Ecole Normale Superieure, Pasteur put together an extensive and multidisciplinary research team that sought to develop vaccines for chicken cholera, rabies, anthrax, and a score of other diseases. For this purpose, he mobilized the necessary financial resources and obtained funds from the national government and agricultural societies. As an academic researcher, Pasteur had an aggressive concern for his scholarly contributions and intellectual property and, to a large extent, he succeeded in keeping the method by which he had produced his vaccines private [90]. Pasteur had also taken out several patents for his methods of manufacturing and preserving wine, vinegar, and beer, and for the vaccines against anthrax and other livestock diseases. He used the royalties from these patents to fund more of his research and build up a pension scheme. Although he had an interest in patenting his methods, treatments, and preventive vaccines, Pasteur was not motivated to commercialize his scientific discoveries and treatments any further, for instance, by

manufacturing and selling vaccines himself or through a new company in which he would have a substantial share [90].

Pasteur was able to link his work on microbes to the interests of clients and stakeholders, using his microbiology laboratory and public demonstrations of the anthrax and rabies vaccines to fuse the interests of the stakeholders with his own drive to advance science and uncover the truth. For Pasteur, this would have been the ultimate source of the power a scientist has over society, in line with Latour's (1983) paraphrasing of Archimedes: "Give me a laboratory and I will raise the world" [91]. In 1888 a grand research centre in Paris was founded as a centre for education and research on infectious diseases. Initially, this Pasteur Institute relied upon private donations from all over the world and the royalties from Pasteur's patents, but at a later stage, when the patent revenues declined, the institute became increasingly dependent on state support [90].

2.3.2 Fritz Hoffmann-La Roche

Unlike Pasteur, who gave us the method of pasteurization (preventing wine and beer from spoiling), a number of preventive vaccines, and a large and internationally well-known research institute in his name, Fritz Hoffmann's fame and recognition lies in the fact that he established an internationally top-ranking life-sciences company and made a fortune during his entrepreneurial career [92]. His family had made its fortune in textile manufacturing and trading and provided him the necessary contacts and financial support he needed at the beginning of his business career. Without any formal training in pharmacology, Hoffmann entered the pharmaceutical industry in 1893 when he joined the pharmaceutical merchant Droguerie. Much to the surprise of the Droguerie's owners and managers, Hoffmann, together with his colleague Carl Traub, spotted an opportunity for in-house development of drugs and expressed their interest in buying out the company's laboratory. In 1894, Hoffmann, Traub, and Company was established; Hoffmann took care of manufacturing and selling a small range of pharmaceutical and chemical products, his father supplied the majority of the start-up capital, and Traub provided the patents.

A few years later, Traub and Hoffmann agreed to break up their business. With financial support from his family, Hoffmann effectively managed to take over and re-launched it as Hoffmann-La Roche and Company in 1898. Hoffmann modernized the business by extending small-batch manufacturing into mass-scale industrial production, pursuing a proactive sales policy (by simultaneously targeting the larger public, chemists, and doctors), and establishing a network of sales agents and distributors throughout Europe and the United States. In early 1900, the company started to shift its research strategy from extracting natural products to synthesizing compounds. Hoffman-La Roche's products were already internationally available; the cough syrup Sirolin, Tubunic, and the fl u treatment for the 1918 epidemic sold particularly well. To obtain more money to recover from World War I and proactively invest in R&D, innovation, and geographical expansion, Hoffmann-La Roche went public in 1919. In the same year, Hoffmann retired from the company's board due to ill health, and he passed away one year later. In the 1920 and 1930s the company had started with the large-scale production of various vitamin preparations and by the 1950s and 1960s had begun introducing tranquilizers, such as Valium and Rohypnol.

Whereas Pasteur was more of an inventor/scientist, Hoffmann was an innovator-entrepreneur who explored and exploited opportunities: He put new discoveries into practical use and brought his pharmaceutical products to the market. Hoffmann was particularly interested in product promotion and paid attention to the whole value chain, from encouraging research and looking into the patentability of a discovery to transforming the invention into a market innovation, producing and packaging it, and advertising and selling it to pharmacists. He also established an international network of businesses supplying the raw materials needed and the relevant sales contacts for his end products. Moreover, he can be considered a pioneer in large-scale manufacturing through standardizing packaging and preserving batch quality.

2.4   Today's Value Chain for Vaccine Development

After discussing the distinctive scientific profiles and different entrepreneurial styles and providing two illustrative cases showing what it means to be an inventor and entrepreneur in the health and life sciences, this second section describes the context of vaccine development in current times. First, the concept of the vaccine development chain is described, introducing several contextual factors that potentially influence the cost and length of product development. Vaccines can be distinguished from other pharmaceutical products on the basis of the inherent feature of the intervention technology: It employs the host's own immune system to attain protection. Second, the value chain of vaccine drug development is evaluated with the actual and potential contributions from scientists, entrepreneurs, and firms in mind: What are/could be their roles in advancing, promoting, and commercializing effective treatments for infectious diseases?

To start, one has to understand the importance of the technology within the vaccine value chain. Epidemiology is the study of factors that influence the spread and control of diseases. It is a macro-level factor in light of the fact that viral infectious diseases are not geographically isolated and their spread is difficult to predict. The influenza epidemic is a perfect example of this. Influenza is a seasonal viral infection that spreads and causes local epidemics during the colder months of the year—autumn, winter, and spring. It has been estimated that during such a seasonal outbreak, 5% to 20% of the population can be infected, and a substantial percentage of these people develop influenza and stay at home for an average of 3 to 5 days [93]. In most cases, the body's own immune system is capable of clearing the virus; however, certain severe and sometimes lethal manifestations and complications can arise, particularly in high-risk groups. These groups include the very young, elderly, and immune-compromised individuals [94].

The societal burden of seasonal influenza is measured in terms of its financial impact, caused by issues such as patient and caretaker absenteeism and a significantly increased demand on medical resources. As a result, in the Unites States alone the annual economic impact of influenza epidemics can reach U.S. $87 billion [93]. This figure is significantly reduced through introducing influenza vaccines and other antiviral compounds. In case of an influenza pandemic, fighting the infection becomes an internationally coordinated event by the World Health Organization (WHO). The latest pandemic originated in Mexico during the first half of 2009, and the economic burden for this country alone was estimated at U.S. $57 million a day [94]. The H1N1 virus, which causes swine influenza (called the

Mexican flu in some countries), was considered harmful because, in addition to the classic high-risk groups, individuals with no increased risk developed serious complications and died from the infection. In case of a pandemic threat, it is crucial that the pharmaceutical industry responds quickly and provides an accurate vaccine product for immunization. When it comes to designing a vaccine against a pandemic threat, WHO collaborating centres provide reference seed viruses. These are subsequently used by the pharmaceutical industry for production of the vaccine. Fierce competition arises as each firm wants to be the first in the market with the vaccine product. In the European Union, the most important vaccine producers during the pandemic vaccination campaign were GSK and Novartis producing Pandemrix and Focetria, respectively. The pharmaceutical value chain unifies all pharmaceutical and biotechnological product research and development, including vaccines, as a common factor. Once a target compound has been identified, it enters a linear development path that eventually results in a commercial product. Development consists of a series of chronological phases governed by national and international legislation (see Appendix).

Since Edward Jenner's cowpox immunization days, the process of developing a vaccine product—or any other life-science drug or medical device for that matter—has become significantly more complex. Since the 1950s, it has taken an average of 10 years longer to complete the value chain and costs more than twice as much as it had previously [95, 96]. As a matter of fact, increasing development times demand even more resources, including financial investment. Estimations of the cost involved for one pharmaceutical product completing the value chain easily surpasses U.S. $1billion [97]. This statistic also compensates for the investment in discontinued projects, yet such calculations do not usually distinguish between new chemical entities and vaccine products. Several explanations for the extended value chain are listed below [98]:

- International harmonization efforts, the process intended to streamline the value chain at a country-to-country level.
- The generation of rules that aim to prevent medical incidents.
- The generation of rules that aim to prevent fraud.
- A rise in public consciousness regarding the realization that vaccine products administered to humans require both ethical regulation as well as adequate business standards.
- Technological resources and theoretical knowledge on the immune system increases experimental complexity.

On the one hand, there are necessary and legitimate reasons for an increase in both the duration and cost of the value chain. On the other, the value chain has to be flexible enough to allow for quick product development and distribution during the event of an epidemic or pandemic. Developing a vaccine product targeting a viral infectious disease is an unmet medical need within an international political setting. With current modes of transportation, a disease can spread to other continents in a few hours (for example, recent outbreaks of SARS and H1N1). Governments, medical facilities, and industries all over the world are affected and have to respond with appropriate strategies. At the project-level, there are two elements that play an important role: the cost of investment and the statistical chance of a product completing the value chain (Figure 2.1). Developing a vaccine is a

lengthy and costly endeavour involving a risk of termination due to unforeseen circumstances [99]. Terminating a project is not an easy decision and represents a burden at the individual and societal level for several reasons. First, the patient population does not receive appropriate treatment. In the case of an infectious disease, human-to-human spread of the pathogen can occur at an uncontrollable rate, posing a public health risk. Second, resources invested in the project are lost. So where does the money come from? A project is financed from several sources including governmental subsidies and venture capitalists, for example. In view of the fact that government subsidies are generated from national taxes, discontinuing a project also affects society at an economic level.

Figure 2.1   Relationship between project success rate (Right) and cumulative milestone investments (Left).
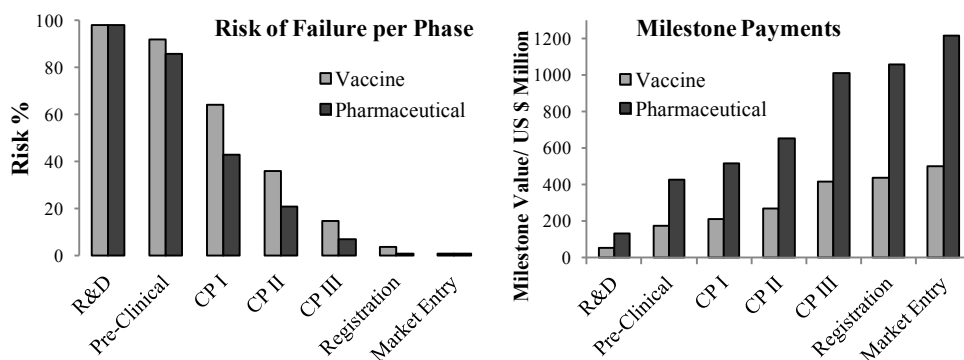
If we regard the value chain as being segmented into various phases, the option of milestone payments for every step are useful as this spreads the risk (see figure 1, right). Nearer the ending of a phase, safety and efficacy data is collected in order to decide whether to continue on to the subsequent development stage. One may believe that after the completion of a phase, when more supportive medical evidence is available, the decision to proceed will become easier. Conversely, there is actually more at stake; it is evident that when dealing with an investment of this magnitude, this inherently raises the pressure to succeed the further along the value chain it is. Risk is usually calculated as a product transition percentage (at market level), indicating the amount of products that make the transition from one phase to the next, with the ultimate goal of reaching the market (see figure 1, left). These types of calculation are usually retrospective analyzes based on historical accounts and are descriptive.

It is believed that the value chain starts with 5,000 to 330,000 candidate molecules during the R&D stage, from which only one molecule attains market approval. By combining both the financial investment and transition rates of a product, we attain micro-level context information in the form of a risk profile (Figure 2.2). This information is highly valuable when making decisions on whether to invest in later phases and whether to continue with the project. As seen in figure 17.2, the further along the value chain, the risk correlates negatively with the investment. However, there is no such thing as 100%

certainty at any moment, and a project can be terminated for any number of reasons [99]. From the financial perspective, it is crucial to discontinue a project as early as possible. Risk is always relative to something; hence, the figure depicts the risk profile for pharmaceutical products as well. In short, vaccines require a lower investment when compared to biopharmaceuticals. Moreover, it has been estimated that for every vaccine candidate that initiates the value chain at preclinical phase, 22% enter the market as commercial products. This percentage is higher for biopharmaceutical products [100].

Figure 2.2 **Relationship between project cost and success rate.**

Each point on the curve corresponds to a particular value chain phase - labelling applies to both curves. Below the graph, there is an indication on the window of opportunity, where the entrepreneur can benefit most (Combining [82, 101-103]).

R&D   Research and Development
PC   Pre-clinical phase
PI   Clinical Trial Phase I
PII   Clinical Trial Phase II
PIII   Clinical Trial Phase III
Rg.   Regulatory authority dossier submission
M.E.   Market Entry
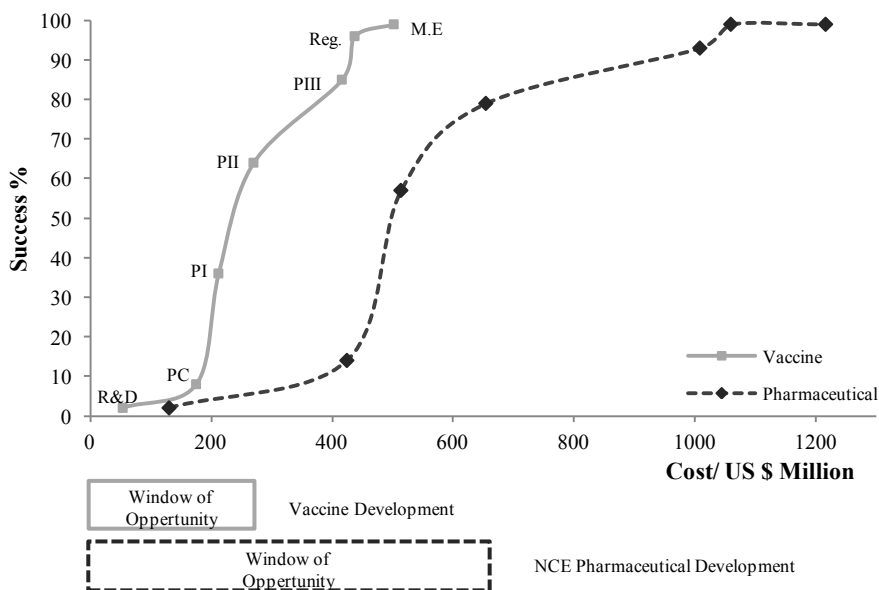
2.5 Today's Entrepreneurs in Vaccines and Other Life Sciences

In a perfect world, each initial product entering the value chain would also complete it successfully. Fortunately for small biotech companies, this is not the case and there is room for entrepreneurs to enter the industry and find a position in the value chain. Entrepreneurial activity in vaccine R&D is closely linked to the concept of productivity and innovation. A standard measure for the productivity of the pharmaceutical industry is the annual license approvals by the regulatory bodies, such as the United States Food and Drug Authority (FDA) or the European Medicines Agency (EMA). The approval of these licenses is critical for market entry and is the ultimate goal when starting a project. Since the 1970s, the biopharmaceutical industry has been haunted by a so-called 'productivity gap,' an increasing amount of resources directed at R&D departments with a seemingly limited number of products entering the market [76]. Contrary to popular belief, when looking at the graph published in literature [104], a positive trend historically has been reported in terms of the productivity of the industry. The data is collected for U.S. pharmaceutical product performance only; however, it is assumed that a similar trend can be observed for any therapeutic category within the global pharmaceutical industry, including vaccines. Nevertheless, it remains a fact that the proportion invested in the value chain compared to the quantity of product approvals is unbalanced. Entrepreneurs can contribute in multiple ways to vaccine development as the various phases of the value chain require different entrepreneurial strategies and skills.

As previously mentioned, Smith and Miner (1983) and Miner, Smith, and Bracker (1992) argue that there are several types of entrepreneur, each with specific managerial motivations and who will establish different firms. Within each stage of the pharmaceutical value chain, all three types remain active throughout the value chain; however, there are certain preferences as to which development stage is most attractive (Appendix 2.7). The overall aim for entrepreneurs in the life sciences is to develop technology, knowledge, or services that increase the efficiency of (certain parts of) the value chain and ultimately strive for market approval. The 'craftsman' is involved with making a better product and is predominantly active during the R&D and preclinical phases, although he or she can contribute during all clinical phases as well. In this case, the craftsman does not have a low level of education or training as the industry is run according to standard operating procedures. An example of a craftsman is the scientist who develops compounds; he/she has excellent knowledge of the product but does not take the target patient population into consideration (e.g., developing a lotion that treats the indication but leaves a yellow stain on the skin).

The opportunistic entrepreneur concerned with building the business is most active within the emergence phase of the industry. Although the risk is high, it is within this time frame that the financial benefit accelerates most steeply, and there is ample opportunity to increase efficiency of the value chain and prevent project termination while doing so. From clinical phase III onward, the value chain is less attractive to entrepreneurs; this phase usually has a set outcome and requires approximately 33% of the total value chain budget[102]. Only under rare circumstances is a project discontinued during a clinical phase III trial. Moreover, a small-to-medium-sized firm does not have the financial resources or physical capacity necessary to complete a phase II or phase III trial and aims to be

acquired, via a merger or acquisition deal, by the pharmaceutical industry as an exit strategy. From this point onward, entrepreneurship continues in the form of 'intra-preneurship' within the larger pharmaceutical company.

The inventor-entrepreneur, known to 'live for inventing,' also benefits from the window of opportunity during the industry's early stages. He or she is not only able to recognize an opportunity but will also create more efficiency in the process. An example of a current initiative from an inventor-entrepreneur is the Artemis Wildlife Health Institute[A]. If considering epidemiology, it has been estimated that approximately 70% of pathogens descend directly from wildlife or domestic animals [105]. With this information, entrepreneurs can unify veterinarian and wildlife centres with existing human R&D research units, for example. By developing this type of multidisciplinary interaction, infectious pathogens can be studied and strategies can be designed to identify pathogen transmission more efficiently and rapidly. More specifically, animal-to-human and subsequent human-to-human transmission can be identified using knowledge about the pathogen's underlying genetic changes as well as the predisposing factors that cause or facilitate these events. In this way, emerging epidemic or pandemic threats to public and animal health can be identified more effectively, allowing for intervention strategies to be implemented in a more timely manner.

2.6   Conclusion

The objective of this chapter was to explore the distinctive contributions made by the academic inventor and the innovative entrepreneur toward the development of vaccine drugs. The complex phenomenon of science-based venturing describes the relationship between scientific knowledge creation, and its effective commercial and societal exploitation by public and private sector. The historical accounts of Pasteur and Hoffmann indicate two different approaches to science-based venturing: The former was invention driven, whereas the latter was more commercially driven. In the pharmaceutical and biotechnological industry, vaccines are considered a fundamental innovation. Historically, on a global scale, vaccination has contributed greatly to decreasing human mortality rates as a result of infectious diseases and maintaining public health, for example, through the eradication of polio. With an annual compound growth rate of 23% since 2004 [106], this therapeutic intervention will remain an essential part of preserving our health in the future.

The main themes of this chapter address the organization of the value chain during drug development and the roles scientists and entrepreneurs play in it. First of all, as a result of certain medical incidents in the past, the necessary rules and legislation governing the vaccine value chain have shaped it into its current lengthy, costly, and rigid format. Nevertheless, in the case of a pandemic threat, governments, industry, and regulators have to react quickly, requiring the value chain to respond with a certain degree of flexibility. This represents a delicate balance, taking into account the fact that vaccines are administered to healthy individuals and high-risk groups and there is a zero-tolerance attitude toward side-effects. Another theme involves the entrepreneur and the risk profile

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[A] Visit: http://www.artemiswildlifehealth.eu/

for vaccine development. Entrepreneurs endeavour to increase the efficiency, innovation, and success of vaccine development during the initial phases of the value chain. Here, entry cost is relatively low and the return on investment is potentially higher, even though there is a high failure rate. Project discontinuation not only represents a social loss (without immunization the spread of infectious diseases cannot be easily controlled) but also societal loss expressed in financial terms. Entrepreneurs are more commonly active during the early stages of the vaccine value chains as this phase offers the main window of opportunity to enter the industry. The fact remains, however, that the investment and productivity trends are not in proportion to one another. Additionally, the value chain is a holistic procedure that requires input from various disciplines and actors. The ultimate goal in life-science venturing is the development of knowledge, technology, and products while abiding by international ethical, safety, and efficacy standards.

2.7   Appendix

Individual level and organizational level entrepreneurial involvement during each phase of the value chain

CRA   Clinical Research Associate, also known as monitor
CRO   Contract Research Organization
TTO   Technology Transfer Office

NA   Not Applicable/ Available
*   For as long as the vaccine product remains in the market
**   Applies to the Netherlands; including credits and special tax breaks

Value Chain Phase	Description	Average Phase Length/ Year	Who is involved; Project Level?	Who is involved; Organizational Level?	Funding Source **	Type of Entrepreneur at Project and Organizational Level	Institutional level
Lead discovery, Selection and Optimization (R&D)	A process also known as Research and Development (R&D). Usually occurs *in silico* (computer simulations), *in vitro* (actual experiments in cells) and *in vivo* (animal models).	NA	Scientists, PhD, Professor	Academia, Governmental, Private Biotech Laboratory or In-house	IP Fund, PreSeed Fund, Venture Capital	Craftsman Inventor-entrepreneur Opportunistic-entrepreneur	TTO, governmental institution
Pre-Clinical Phase	Including various sub-phases *in vivo* (experiments in disease animal models) to determine preliminary quality, toxicity, pharmacodynamic and dosage profiles.	1.5	Scientists, PhD, Professor	Academia, Governmental, Private Biotech Laboratory or In-house	Proof-of-Concept Fund, Seed Fund, Venture Capital	Craftsman Inventor-entrepreneur Opportunistic-entrepreneur	TTO, governmental institution
Clinical Development	Introducing the drug in healthy human volunteers and patients to establish safety, efficacy and dosage profiles. This step is split-up into three phases; I (healthy volunteers), II (small group of target individuals) and III (larger group of target individuals).	Clinical Phase I 2.5	Physician, Scientist, CRA	Bioventure, CRO, In-House	Valorization Grant, Venture Capital	Inventor-entrepreneur Opportunistic-entrepreneur	TTO, governmental institution
		Clinical Phase II 2.8	Physician, Scientist, CRA	Bioventure, CRO, Hospital, In-House	Biotech Firm, Venture Capital	Opportunistic-entrepreneur	
		Clinical Phase III 2.6	Physician, Scientist, CRA	CRO, Hospital, In-House	Biotech Firm, Venture Capital		
Approval Phase	The application for a license has to be submitted by the biotechnology companies to competent authorities. Only after approval can the product enter the market. In America the FDA, and in Europe the E.M.A. decide on market entry.	2	Marketing and Legal	Pharmaceutical Industry	Pharmaceutical Industry	Large established firms Corporate entrepreneurs (Intrapreneurs)	Pharmaceutical Industry
Marketing Life-Cycle	The process which allows the product to be distributed to the target population.	NA *	Marketing and Legal	Pharmaceutical Industry	Pharmaceutical Industry		
Post-Marketing Approval	Even after the product has entered the market, the product is watched closely for any extremely rare side-effects.	NA *	Physician, Scientist, Marketing and Legal	CRO, Hospital, In-House	Pharmaceutical Industry		

Chapter Three: The Gold Industry Standard

Risk and Cost of Drug Development Revisited

Abstract
Gold dimensions of pharmaceutical drug development indicate that it takes on average 11.9 years, with an investment around US$ 0.8 Billion, to launch one product on the market. Furthermore, approximately 22% of the drug candidates successfully complete clinical testing. These universally acknowledged proportions largely originate from one single, much cited publication; Dimasi et al (2003). However an additional six articles describing new chemical entities (NCE) development were identified, which contain little, if any, information on vaccines. Published cumulative success rates range from 7% to 78% and investments calculations span US$ 0.8 to 1.7 Billion. Obviously this disserves further clarification?

Pronker, ES
Weenen, TC
Commandeur, HR
Claassen, E
Osterhaus, ADME

3.1   Introduction

There appears to be a state of contradiction within the pharmaceutical industry; while more resources are being directed towards research and development (R&D), the number of market approved products does not seem to keep an equal pace [107]. This phenomenon, also referred to as the productivity gap [108], only considers the market entry level of the product development value chain. The value chain describes the chronological phases a drug completes to determine its safety and efficacy profiles, and consists of; target identification, lead selection, pre-clinical phase, clinical phase (I, II and III), registration, market approval and post-marketing clinical phase IV. Development up to clinical phase III is covered in this article.

Possible explanations for this gap include targeting more complex diseases and dealing with stringent regulatory processes [27]. Nevertheless; technological innovations in the first two phases – resulting in efficient high through-put screening of candidate compounds – does not limit the input end of the value chain, leading us to conclude that obstacles to the pharmaceutical industry's productivity must lie elsewhere.

During both pre-clinical and clinical stages, the industry's productivity can be evaluated using the basic parameters of length, risk and cost of the individual value chain phases. Given that development timelines have stayed reasonably constant since the 1990s [109], risk and cost aspects of vaccine and drug development are subjects of debate. For example, information on the risk of drug development is crucial when deciding on project continuation or discontinuation, and is usually expressed as a phase transition ratio. The cost associated with pursuing the launch of one product is bound to increase over time, at least in part due to the sobering reality that each success story has to cover the expenses associated with the discontinued programmes [107]. The pharmaceutical industry faces the continuing challenge of rendering the value chain as efficient and productive as possible, through reducing overall attrition rates and costs, while remaining innovative and competitive in multiple disease areas.

Commercial vaccine and drug development can be described using the following gold parameters addressing the length, risk and cost of the value chain; one successful product has an average development timeline of 10 to 16 years, with a 22% chance of completing the clinical phases (Clinical trials phase I, II and III), and requires an investment that easily surpasses the US$ 0.8 Billion [110, 111]. As these figures are largely based on little more than a single publication by Dimasi et al. [110], we conducted a literature review that resulted in an additional six relevant papers. In view of the largely conflicting data presented in the respective publications, we critically evaluated the methodologies used and the estimates of the risks and costs associated with vaccine and drug development.

3.2   Methodology

The literature scan was conducted using a combination of Metapress, Pubmed, Google Scholar and Scirus public search engines, applying relevant search terms on the theme, including risk profile, new chemical entity (NCE), pharmaceutical value chain (PVC), drug

development, attrition-, transition-, success-rate, and combinations thereof[A]. Relevant peer reviewed articles published since 1995 were selected based on content. Publications referencing the risk and cost statistics directly from Dimasi et al. [110, 111] were excluded.

3.3   Results

3.3.1   *Drug development success rate*

All seven articles report figures on drug development success rates, yet the results are distributed between 7% [112] and 78% [113] (Figure 3.1). Such dramatic range in observations suggests that calculating the productivity for the entire pharmaceutical industry is challenging and perhaps sensitive to multiple variables. Some articles are more detailed than others when it comes to describing the methodology and considerations for estimating the cumulative risk of drug development (Table 3.1).

Figure 3.1   Drug development cumulative success rates

Measured from the start to the end of the measurement. Sorted by probability of success, as reported in literature [27, 110-115] Results are not indicative for an approval trend over time.
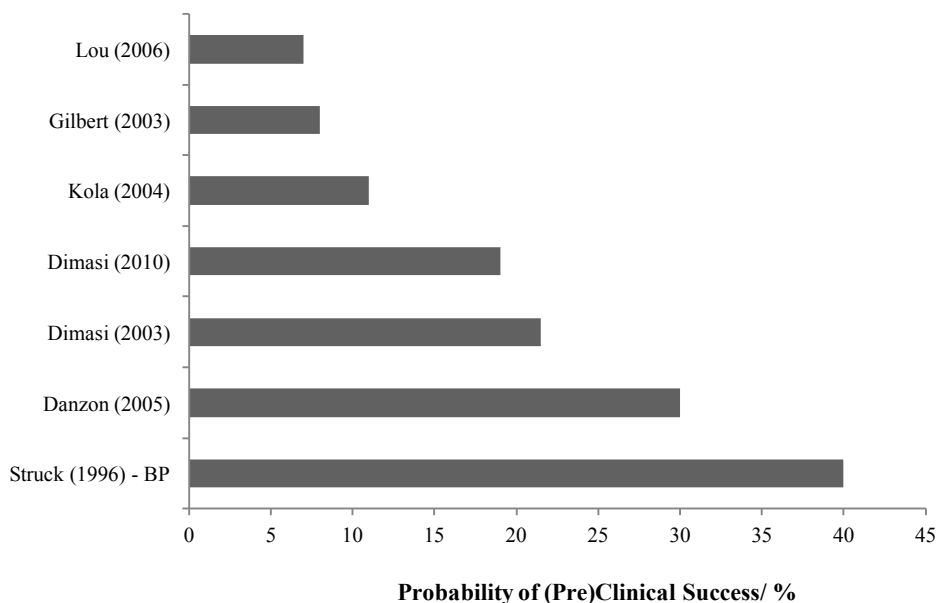
[A] Search performed in September 2010

A possible explanation for the observed range can be attributed to the sources from which the data sets were compiled. Some authors used a single source to develop the data set, referred to industry-sponsored resources or to private communications. Furthermore, it is unclear in most publications which types of NCEs are evaluated and to what extent vaccines are taken into account.

Second, most publications do not justify the sample selection procedure. Various time-frames have been selected for review, ranging from a three-year window [112, 114] to a thirteen-year period [113]. The quantity of compounds selected for analysis varies from 13 [114] to 1910 [113]. Moreover, some articles include preclinical phase in the calculation, whereas others exclusively analyze the clinical phases.

As a final point, the methodology of analysis in most publications is unknown. In addition, some research groups did not clarify whether the effect of a third variable was taken into consideration. Data stratification by clinical phase and therapeutic class [27, 111, 113] product origin [111, 112], firm experience [113, 116] or product type [115], reveal significant variations in compound success rates.

3.3.2 Drug development cost

The cost for developing a NCE along the pre-clinical and clinical phases is usually classified information, not readily disclosed by pharmaceutical companies. Hence the estimates in the selected publications are based on assumptions, making the results sensitive to reporting bias [117].

In three of the previously identified articles, estimates on the cost of developing a NCE are reported – US$ 0.8 [110], 0.9 [27] and 1.6 Billion [114]. The research groups defined the risk of development and the cost involved independently from each other. Success rates are also graphed, providing an indication of the risks involved with the investment (Figure 3.2).

The Dimasi paper [110] has the most descriptive methodology. The data published in this article has been cited by many sources, including recent PhRMA reports [102]. It has largely been adopted by the pharmaceutical industry as a gold standard, even though the credibility of the results have been challenged [117, 118]. The calculation is based on 68 NCE using an interview tool, combining out-of-pocket and real cost for products in pre-clinical phase through to entering clinical phase III. The other two research groups quote figures from commercial reports for which methodologies remain confidential.

Figure 3.2   Cumulative investment for a NCE completing the clinical phases (Bar graph), including the cumulative risk (plotted point) [27, 110, 114].

All cost calculations exclude vaccines. The graph does not show the trend; the lower the investment, the higher the success rate. Instead, these are three independent cost and risk calculations.
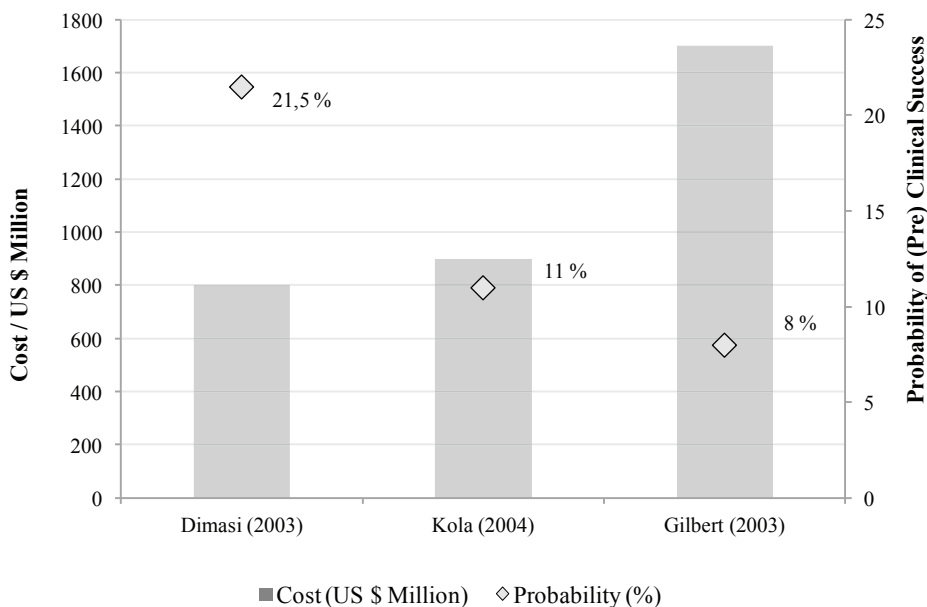
3.4   Discussion

As indicated in the leading articles, there is no standardized format for NCE risk and cost calculations. Cumulative success rates indicate substantial differences ranging from 7% to 78%. If against all odds the compound reaches the market, it will have required an investment of US$ 0.8 Billion or more. We propose a few justifications for the range in published parameters.

First, NCE products cannot be generalized. Most publications use aggregate data neglecting potential third variable influences on the success rate. This has been demonstrated in articles differentiating between therapeutic class or the origin of the molecule, revealing significant diversified success rates across categories.

Second, data is collected from a range of sources. Sometimes including combinations of; commercially available marketing reports, scientific publications, industry sponsored databases, and confidential resources. Research gains credibility when multiple sources are consulted, yet considering the limited justification for the choice of sources and the fact that data from the latter two options makes replication challenging, external validity is questionable.

In most publications, the chosen parameters building the dataset are left unexplained. For example opting for a 2-year observation window when development takes on average 10 years or more. Some articles do not explain how data on failed or terminated projects have been considered for the success rate and cost calculations. Moreover it is unspecified which processes are included in the pre-clinical phase. It proved unclear in most cases whether the parameters are due to practical limitations – such as data availability – or to predetermined variables. Without such transparency, ambiguous data set descriptives or calculating protocols challenge the scientific quality of the statistics, and it remains debatable whether the product transition rates published are representative for the global pharma industry.

Finally one may question whether it is even possible to accurately determine the cost for the development of a drug or vaccine. It is imaginable that larger firms have "fluid" resources and can easily allocate them to a priority programmes when compared to a company with only a limited number of products in the portfolio. The current industry descriptor, by Dimasi et al. [110], analyzes risk and cost for the top pharmaceutical companies. Without randomization of the product type or sponsor company (size), the results are prone to selection bias.

It can be concluded that in general, developing drugs involves high attrition rates and requires large investments. In addition it is challenging to accurately determine the transition rates and cost for a product in pre-clinical and in clinical development, to represent the behaviour of development for the entire pharmaceutical industry. All articles cited in this review paper present an analysis of their unique dataset, and the results should not be compared to one another but interpreted as indications at best. Considering that determining the risk and cost for NCE and vaccines requires a more holistic approach, we would argue that there is no gold standard.

Table 3.1   Dataset specifics for the analysis of drug development success rates, as reported in literature [27, 110-115]

Source	Compound in analysis/Count	Type of Compound	Time frame/years	Other inclusion criteria	Vaccines?	Source of data	Calculation	Stratification	Result
Danzon (2005)[113]	1910	NCE	1988-2000/13	• Molecules in PI, PII and PIII • Compounds developed in US only	N.A.	R&D Adis Insights Database, Windhover Information and Pharmaprojects	• Logistic regressions • Terminated projects included	• Company experience • 13 therapeutic areas	• 30 (Respiratory) • 78% (Hormones)
Dimasi (2003)[110]	538 68 for cost calculation	NCE	1983-1994/12	• Molecules in PC, PI, PII and PIII • All self-originated • First in human during 1983-1994 • Mostly from top 20 firms based on pharmaceutical international sales	1 vaccine included in cost calculation	Tufts Centre for the Study of Drug Development (CSDD) database + commercial sources and survey instrument	• A two-stage statistical estimation for risk calculation. • Combining out-of-pocket and real cost based on interviews • Terminated projects included	• None	• 22%
Dimasi (2010)[111]	1738	NCE	1993-2004/12	• Molecules in PI, PII, PIII and registration • NCE pipeline of top 50 pharmaceutical firms based on 2006 sales	Excluded	IMS R&D Focus database, iDdb3, Pharmaprojects, Tufts CSDD, surveys, regulatory documents and internet search	• A transition ratio • Terminated projects included	• 8 therapeutic areas • Origin of product	• Average: 19%
Gilbert (2003)[114]	13	NCE	1995-2000/6 2000-2002/3	• Molecules in PC, PI, PII and PIII to Launch • Strengthened by FDA report; Biological License Applications/ New Molecular Entities	N.A.	Bain Drug Economic Model 2003	• Unknown calculation for risk and cost • Terminated projects; unknown	• Historical time	• 14% (development between 1995-2000) • 8% (development between 2000-2002)
Kola (2004)[27]	N.A.	NCE	1991-2000/10	• Molecules in PI, PII, PIII and registration • NCE from 10 biggest EU and US pharma firms during time-frame	N.A.	Datamonitor in the Pharmaceutical Benchmarking Study.	• Unknown calculation for risk and cost • Terminated projects; unknown	• 9 therapeutic areas	• Average: 11% Range; • 5 % (women's health) • 20 % (cardiovascular)
Lou (2006)[112]	432 self-originated 86 in-licensed	NCE	1998-2000/3	• Molecules in PI, PII, PIII and successful market entry	N.A.	Centre for Medicinal Research (CMR) R&D Fact Book 2005/6	• Unknown calculation • Terminated projects; unknown	• Origin of product	• 7% (self-originated) • 14% (in-licensed)
Struck (1996)[115]	577 vaccines + unknown quantity BP	Vaccine and NCE/BP	1983-1994/10	• Vaccines and BP in PC, PI, PII, PIII, Registration and Launch	Included	Pharmaprojects Database	• Transition probabilities and chi-square testing • Excluding failed candidates	• Product type	• 40% (BP) • 22% (Vaccines)

NA   Not Available
BP   Biopharmaceutical
NCE   New Chemical Entity

PC   PreClinical Phase
PI-III   Clinical Phase I-III

Chapter Four: Risk in Vaccine Research and Development Quantified

Abstract

To date, vaccination is the most cost-effective strategy to combat infectious diseases. Recently, a productivity gap affects the pharmaceutical industry. The productivity gap describes the situation whereby the invested resources within an industry do not match the expected product turn-over. While risk profiles (combining research and development timelines and transition rates) have been published for new chemical entities (NCE), little is documented on vaccine development.

The objective is to calculate risk profiles for vaccines targeting human infectious diseases. A database was actively compiled to include all vaccine projects in development from 1998 to 2009 in the pre-clinical development phase, clinical trials phase I, II and III up to Market Registration.

The average vaccine, taken from the preclinical phase, requires a development timeline of 10.71 years and has a market entry probability of 6%. Stratification by disease area reveals pandemic influenza vaccine targets as lucrative. Furthermore, vaccines targeting acute infectious diseases and prophylactic vaccines have shown to have a lower risk profile when compared to vaccines targeting chronic infections and therapeutic applications.

In conclusion; these statistics apply to vaccines targeting human infectious diseases. Vaccines targeting cancer, allergy and autoimmune diseases require further analysis. Additionally, this paper does not address orphan vaccines targeting unmet medical needs, whether projects are in-licensed or self-originated and firm size and experience. Therefore, it remains to be investigated how these - and other - variables influence the vaccine risk profile. Although we find huge differences between the risk profiles for vaccine and NCE; vaccines outperform NCE when it comes to development timelines.

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4.1 Introduction

Human life expectancy has increased due to the implementation of hygiene, sanitation and vaccination. Immunization strategies - of which the use of vaccines is the most important - have prevented more premature deaths, permanent disability, and suffering, in all regions in the world, than any other medical intervention [5, 119-121]. Vaccines are the most cost-effective strategy with the potential to prevent - or even cure - acute and chronic infections, allergic conditions, auto-immune diseases and cancer [82, 122]. Prophylactic and therapeutic vaccination leading to both individual and herd immunity as well as symptom relief during disease progression respectively, will continue to be of fundamental value in maintaining public health in the future [123, 124].

Unfortunately, as with the pharmaceutical industry, also the biotech sector is affected by the so-called productivity gap[A] [76, 77]. Developing a human vaccine from the preclinical phase to registration[B] requires an increasing average investment of approximately US$ 200 to 900 million [82]. However, merely 22% of the initiatives were forecasted in 1996 to successfully reach the market after 10 years of development [125, 126]. This imbalance is to a large extent caused by rising cost of research and development (R&D), biological and technical challenges associated with targeting more complex diseases, competition with better standards of care, larger scale of clinical studies to prove safety and efficacy and last but not least an increasingly stringent regulatory environment [97, 99]. From the perspective of the patient, and in financial terms: the subsequent attrition rate is substantial and should be improved.

Value chain descriptives - including, but not limited to; phase duration and transition rates- are important parameters for investors seeking strategic financial advice. The result of combining these two dimensions is a relatively accurate physical indication of the productivity at different development stages. The current benchmark on methodologies for determining risk profiles[C] is published by Dimasi *et al* (2003) [97], and applies to new chemical entities (NCE). To date, there is limited documentation on vaccine development. Two articles in particular - one from 1996 [127] and a more recent publication from 2011 [128] - focus on value chain descriptives comparing NCE and vaccine profiles. We intend to take the analysis one step further and introduce the additional variable of the target infectious agent.

[A] The productivity gap describes a situation within an industry whereby the invested resources do not match the expected product turn-over

[B] Also known as the value chain; the consecutive development stages a vaccine or medical compound progresses through to accumulate value and become established as a safe, effective and qualitative product

[C] Risk profile; combining data on average phase duration with rates of projects transitioning between value chain phases

4.2   Objectives

The present paper offers an empirical analysis on the value chain risk profiles for human vaccines in development from 1998 to 2009. We hypothesize that current vaccine risk profiles behave in a pattern similar to those described for NCEs: since 1983 to 1994 [129] the overall phase duration is postulated to have lengthened but the market entry probability is expected to remain relatively constant [130]. Moreover, by stratifying data according to infectious disease areas, we aim to identify the development stages during which attrition rates are highest. In the competitive landscape where resources are limited, the overview allows for vaccine developers and investors to anticipate common project-level challenges for the particular disease area.

4.3   Methodology

Our methodology and assumptions are based on Struck [131], and Dimasi [132]. Data is collected on five value chain phases on the basis of availability, observing human vaccines in development from 1998 to 2009[A]. An active research strategy is chosen to develop the proprietary dataset, cross-referencing various sources including; commercial database (Medtrack[B]), governmental sources, company sources open to the public, official press statements and scientific publications.

Using the commercial database as a starting point, a total of 902 vaccine candidates during any stage of development were included in the dataset[C]. It was assumed that the database is current and contains an accurate record of all vaccine projects, making randomization unnecessary. Consequently the data was filtered according to specific in- and exclusion criteria (Table 4.1). By defining the dataset we assumed that phases do not overlap, and that each vaccine progresses through the same stages in chronological order.

Phase duration was determined by the average number of years a vaccine candidate takes to complete a development phase. Discontinued projects were not included in this calculation since the decision can occur at any moment distorting results; 456 vaccine projects remain eligible. For practical reasons we consider a year to have 360 days.

The second element of the risk profile constitutes the transition probability, which was determined by applying the formula as described in [133]. Furthermore, the cumulative transition ratio is taken to represent the market entry probability. It indicates the proportion of vaccine candidates that developed successfully from PC to the highest attainable development phase. All vaccine projects in the dataset were included in these calculations.

[A] The five development phases included in the analysis; Preclinical (PC), Human Clinical Trials Phase I-III (PI-III) and Regulatory submission (RS). Discontinued projects (D) are also included. Where available, data is updated to 2010.

[B] Medtrack © is opted due to accessibility, and is compatible with Pharmaprojects ©.

[C] Data was collected on the 12th of May 2010 showing 1495 entries. By excluding products on the market, in post-marketing trials, or where no details were found (NA), 902 unique products remain.

Lastly, data was stratified according to therapeutic area for investigating this third variable influence on the phase duration and transition probabilities. Furthermore, within this infectious disease category, data on vaccines against acute infections, chronic infections, preventative indications and therapeutic indications are analyzed separately. Nevertheless, in order to recognize the significance of the disease area, risk profiles are placed into context of the disease burden and invested resources. The estimated patient population is taken to represent the former aspect; whereas the latter was measured by total sum of the value of merger and acquisition (M&A) deals[A]. The disease areas covered by the majority of vaccine projects are presented in this paper.

Table 4.1   In- and exclusion criteria for fine-tuning the dataset, inspired by [110, 111, 115]

Inclusion criteria	Exclusion criteria
EMPHRA Code J7 = human vaccine product, prophylactic and therapeutic.	Vaccine product undergoing post-market clinical trials for additional indications
Vaccines target human infectious diseases caused by; viral, bacteria, fungi, parasites, bacterial toxins and unspecified infectious agents.	Vaccines targeting cancer, allergy and auto-immune indications.
The database entry has descriptive information on the product; sponsor company, therapeutic area, at least one date indicating the state of the current development phase	The vaccine product cannot be found on at least one other source. Except for products in PC or D phases, as these are underreported
Product is in the following phases according to the database; PC[B], PI[C], PIID, PIII[E], RS[F], D[G].	Products in the following phases according to the database: M[H], PM[I], NA[J], F[K].
Start of PC phase in 1998	Duplicate entries

[A] The commercial database Pharma ETrack © is consulted on financial statistics of M&A. The sum of M&A activity in US $ Million since 2004 is calculated as an indication for the amount of resources the biotech industry invests in the particular disease area.

[B] Preclinical Phase

[C] Human clinical trials Phase One

[D] Human clinical trials Phase Two

[E] Human clinical trials Phase Three

[F] Regulatory submission to allow market entry

[G] Projects discontinued for any reason during any stage of the following stages of vaccine development; PC, PI, PII and PIII

[H] Market phase

[I] Post-marketing, also known as human clinical trials phase four

[J] No information available

[K] Failed or terminated vaccine products. In other words, products that have received regulatory market approval, but have been withdrawn from the market for any reason.

4.4 Results

The filtered dataset contains 605 unique human vaccine candidates during any stage of development, from 188 individual firms covering over 60 therapeutic areas. The risk profile for the average vaccine in development from 1998 to 2009 only partially behaved as predicted (Figure 4.1, black curve); the timeline has lengthened by 0,71 years, yet the cumulative success rate is lower at an estimated transition probability of 0,07 (Table 4.2). On account of the sizeable standard deviations, we would advocate that risk profile parameters delineating the entirety of the dataset should only be interpreted as an indication for the general development trend of the vaccine manufacturing industry.

When dividing the data according to the third variable - areas of therapeutic intervention - 49% of the vaccine pipeline covers 5 conditions. Furthermore, Japanese Encephalitis (JE) vaccine projects are highlighted due to multiple recent product approvals. These include; Ixiaro © (Intercell AG, also known as Jeev © and Jespect ©, available since 2009 in various countries), and beyond the scope of the dataset Encevac © (Kaketsuken, in Japan since Jan 2011) and Imojev © (Sanofi, available in Australia and Thailand since July 2011). The remaining disease areas are not represented by a sufficient quantity of vaccine projects to attain statistically significant comparisons.

By far the most lucrative business opportunity is created by pandemic influenza. In this saturated environment, efficiency is the key word if vaccine manufacturers desire to maintain a competitive advantage. As the current manufacturing capacity for influenza vaccines is limited at 900 million dosages [134], innovations are namely pursued in areas including adjuvant development, delivery system and manufacturing technology [135]. Nevertheless, pandemic influenza vaccine preparedness is a unique and rare situation that should not be compared to vaccines targeting other disease areas.

Pandemic influenza preparedness efforts are largely aligned with World Health Organization's advice to national governments on societal, antiviral and vaccine strategies, based on monitoring the threat-level of emerging potential pandemic influenza viruses [136]. Since purchasing vaccines for immunization campaigns is coordinated by national governments, they are responsible for ensuring sufficient access from the early stages of an influenza pandemic onward. Over the past few decades, several governmental bodies followed the WHO preparedness advice and proactively sought advanced purchase agreements with vaccine manufacturers. Such agreements led vaccine manufacturers to anticipate an increasing demand for influenza vaccines, and as a result they invested in expanding their manufacturing capacity. Furthermore, during the 2009 H5N1 influenza pandemic, vaccine acquisition by individual governments proved to be an inefficient system, and the European Committee (EC) responded by establishing a joint procurement initiative for future pandemic threats in November 2011 [137, 138]. Obviously the sustainability of such provisions is largely dependent on the political will and compliance of individual member states and it probably will be hard to implement in the current era of 'post-pandemic fatigue.'

Figure 4.1   Risk profiles for the selected disease areas,

Risk profiles Combine phase duration with the cumulative transition probabilities as indicated by market entry probabilities. Rank order indicates quantity of projects in data set. Data points are labelled on the All Data curve; this labelling also applies to the other curves.
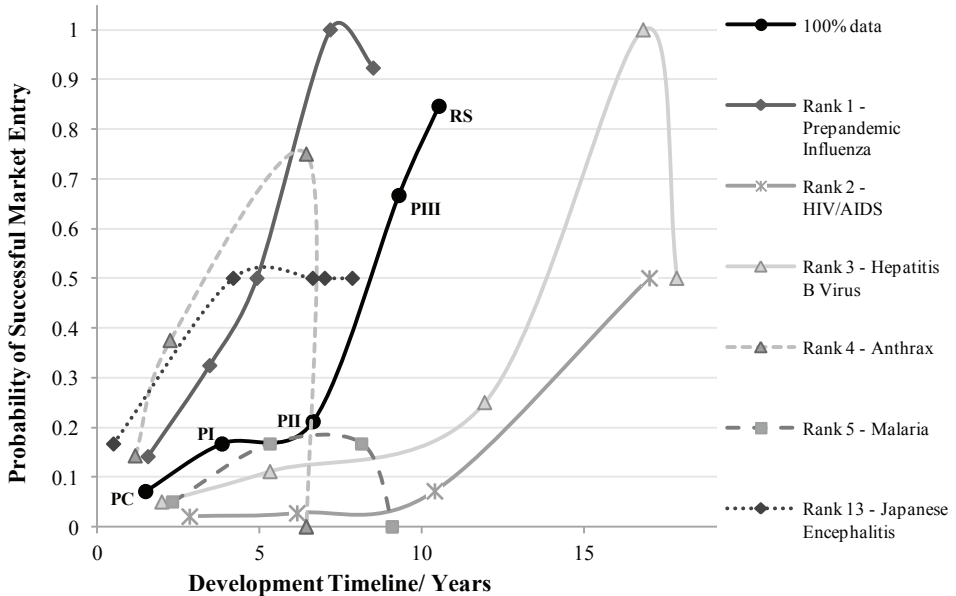
Additionally, JE represents an attractive target for vaccine developers; with merely 11 firms in our dataset investing in R&D, over 1 in 10 initiatives successfully attain regulatory submission phase. The short and steep risk profile presumes half the candidates from PC progress to subsequent PI trials. Nevertheless, due to the low number of candidate vaccines in later stages of development, we believe the timeline is underestimated.

The foremost challenge in vaccine development is reducing the average transition rate from clinical phase II to III. Between these value chain phases the risk profile incorporating all data has an estimated transition probability of 0.21. It represents the highest attrition rate when compared to the productivity of the other phases. Both Anthrax and Malaria risk profiles confirm the bottleneck, as project development activities do not advance beyond PIII. The phenomenon has been recognized in NCE development, and we believe the underlying mechanisms and explanations are also applicable for vaccines[139-141].

A second major obstacle is a successful transition from clinical phase III to regulatory submission. Such bottlenecks are evident in Pandemic Influenza, and Hepatitis B vaccine (HBV) risk profiles, whereby the attrition rate for HBV candidates is calculated at an astonishing 50%. HIV/AIDS projects are also affected by significant attrition rates between these stages. Reasons for submission failures have been described for NCEs, and we assume similar arguments are relevant[142].

Data was further granulated into vaccines targeting acute versus chronic indications and prophylactic versus therapeutic applications (Figure 4.2). According to the dataset, vaccines targeting acute infectious diseases, as well as prophylactic vaccines clearly have a lower risk profile when compared to vaccines targeting chronic diseases or therapeutic applications.

Figure 4.2   **Vaccine risk profile granulating acute versus chronic infections and prophylactic versus therapeutic vaccines.**

Groups are stratified from 100% of the data from the dataset. Percentage per group included.
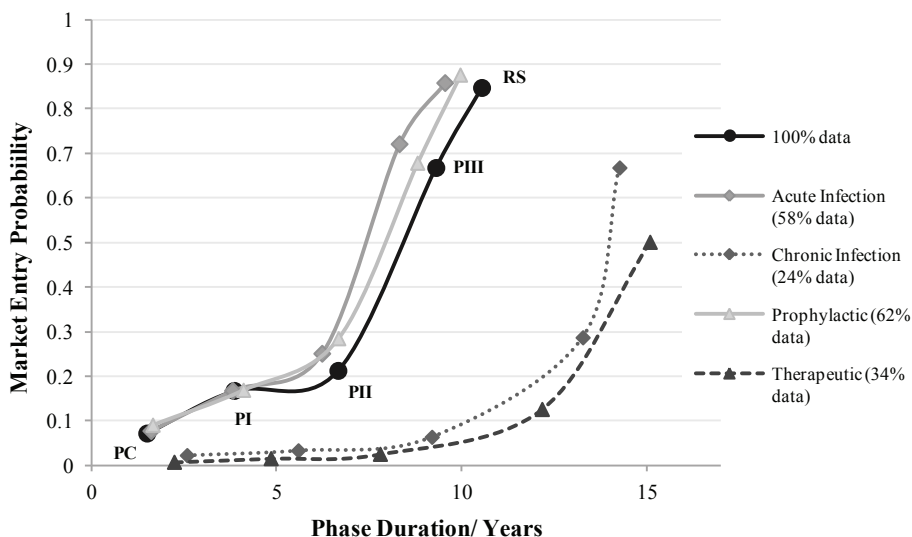
As a final observation: it is generally assumed that a higher disease burden - preferably in the industrialized world [143] - is an incentive to dedicate resources to that particular disease area (Figure 4.3; Table 4.2). As an example of the opposite being the case sometimes: 4% of vaccine development projects target anthrax, while the infection is highly uncommon and related to biological-warfare [144].

4.5   Conclusion

Risk profiles are important descriptive tools providing indications on possible future vaccine project outcomes, essential for strategic decision making. In general, the more recent vaccine development projects from 1998 to 2009 showed a longer timeline with a lower probability of market entry than those from 1983 to 1994 [145]. What could partially explain the increased phase length could be the fact that the ICH-E6 Good Clinical Practice guidelines came into effect after Struck's publication in 1996, which has influenced clinical research on a global scale. However, we feel that the phase lengths calculated are not fully representative for the actual situation. Certain preliminary R&D activities - such as *in silico* lead selection and toxicity screening - taking place prior to patenting are not represented in the dataset. We believe that when these procedures are

taken into consideration, the actual development timeline is expected to be even longer still.

Additionally, the lengthening timelines for vaccine development may be influenced by the fact that the so-called 'low-hanging fruits' has already been picked. Data confirms that the majority of vaccine R&D projects encompassing incremental innovations targeting disease areas with known correlates of protection have a shorter development timeline when compared to more radical vaccine innovations [146]. Nevertheless, vaccine timelines remain significantly shorter when compared to NCE development.

Figure 4.3   Combining the cumulative success rate with the contextual factors of disease burden and size of investment (indicated by the size of the bubble)
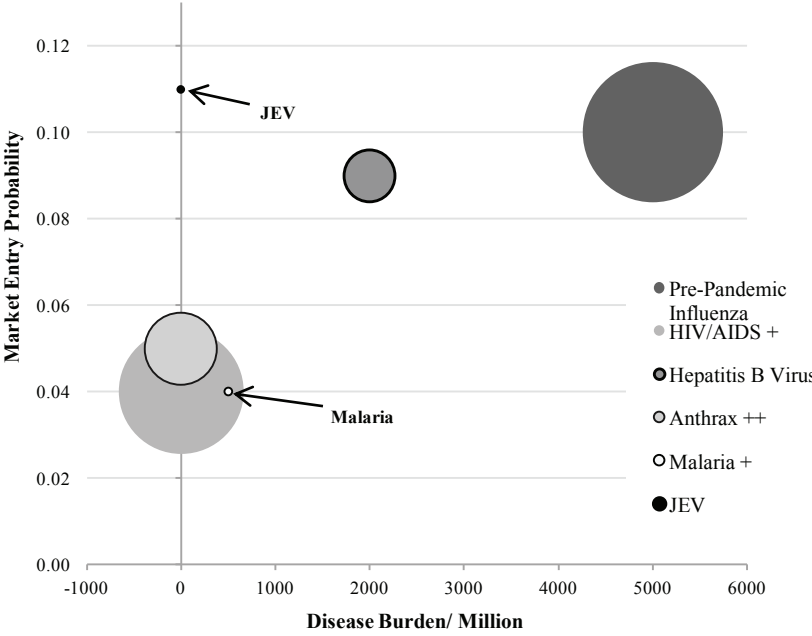
Clarifications for the discrepant transition probabilities between our dataset and previous articles expediently relate to data collection methodologies. Moreover, stratifying data according to acute or chronic indications as well as therapeutic or prophylactic application revealed significant variations in transition success. This confirms that one risk profile cannot represent the productivity of the overall vaccine development field, and the effect of a third confounding variable is essential information.

Essentially, infectious diseases are different from cancer, and both are fundamentally different from allergy and autoimmune diseases with respect to the mechanisms of pathogenesis, immunity as well as the approach and difficulty of vaccine development. Consequently,   vaccine   development   for   infectious   diseases,   cancer,   and

allergy/autoimmunity should be analyzed separately. Moreover, this paper does not address orphan vaccines targeting unmet medical needs, whether projects are in-licensed or self-originated and firm size and experience [99, 147, 148]. Therefore it remains to be investigated how these other variables influence the vaccine risk profile.

Vaccine development is a risk intensive exercise and requires substantial investments. As indicated by the risk profiles: the ratio of success to failure is in favour of the latter. Both the burden of disease and the magnitude of invested resources into a project targeting a specific infectious agent do not correlate with a higher success rate. Substantially resources are dedicated to HIV/AIDS, even though within the scope of our dataset there are no regulatory approved vaccines. It is interesting to note that preventive vaccine development against JEV - a virus that causes acute infection - may not be considered such a lucrative target as the market size is too limited to guarantee a rapid return on investment. Obviously other criteria are used for vaccine target selection [149, 150]. These high rates of attrition need to be reduced in order to sustain business case growth [151], and respond appropriately to public health demands.

Several considerations apply to this study. First, we have assumed that the database on commercial vaccine development - on which the dataset is based - keeps an accurate record of all vaccine development projects currently in any phase of development. The dataset we compiled is unique; however the explicit delineation of methodologies should allow other research groups to replicate procedures. Additionally, phase lengths are influenced by the spread of the data points. The majority of the vaccine development dates (>50%) were collected after the year 2000 implying the spread of points is not equally distributed within the dataset. This either suggests that the earlier years of the selected timeframe are underrepresented, or that the actual quantity of projects has increased over the years.

This paper provides a descriptive historical account of vaccine development between 1998 and 2009, and does not have the ambition to forecast any trends. Moreover we have not addressed the numerous reasons that may lead to project termination, and do not disregard the necessary legislative requirements in the development of ethical, safe, effective, and high quality vaccines.

Table 4.2   Table summarizing calculations of phase duration and transition probabilities for selected vaccine target disease areas.

DUR   Duration in years
SD   Standard Deviation
TR   Transition rate probability
+   Projects do not transition from clinical trial phase III to regulatory submission phase
++   Projects do not transition from clinical trials phase II to clinical trial Phase III

Disease Area	All Data			Pandemic Influenza		HIV/AIDS +		HBV		Anthrax ++		Malaria +		JEV	
Phase	DUR/ Yr	DUR SD/ Yr	TR (P)	DUR/ Yr	TR (P)	DUR/ Yr	TR (P)	DUR/ Yr	TR (P)	DUR/ Yr	TR (P)	DUR/ Yr	TR (P)	DUR/ Yr	TR (P)
PC	1,50	1,89	0,07	1,57	0,14	2,86	0,02	2,00	0,05	1,18	0,14	2,32	0,05	0,51	0,17
PI	2,48	2,12	0,17	1,90	0,32	3,31	0,03	3,33	0,11	1,08	0,38	3,01	1,17	3,69	0,5
PII	2,86	2,45	0,21	1,50	0,50	4,24	0,07	6,61	0,25	4,20	0,75	2,82	1,17	2,45	0,5
PIII	2,64	2,19	0,67	2,26	1,00	6,61	0,50	4,89	1,00	-	-	0,95	-	0,37	0,5
RS	1,24	0,79	0,85	1,32	0,92	-	-	1,03	0,50	-	-	-	-	0,85	1
% of data		100			21,65		12,89		4,96		4,46		4,13		1,82
Rank based on % data		N.A.			1		2		3		4		5		13
Total Duration PC-RS (Yr)		10,71			8,51		17,02 +		17,86		6,44 ++		8,07 +		7,87
Disease Burden	N.A.			1-5 Billion [152]		3,3 Million [153]		2 Billion [154]		Uncommon [144]		3-500 Million [155]		50,000 [156]	
M&A[A]	N.A.			116.000		91.120		15.600		30.700		350		77	

[A] Merger and acquisition, deals in US$ Million since 2004

Chapter Five: Improving the quality of drug research or simply increasing the cost?

An evidence-based study of the cost for data monitoring in clinical trials

Abstract
Aim: Procedures for verification of data from clinical studies are intended to maintain reliability for clinical trial results. Guidelines or legislations relating to clinical data management are of limited value and no study has yet demonstrated its effectiveness.

Method: Sponsor queries and dual entry procedures from one CRO on three different phase I trials are analyzed on content, impact and cost.

Result: In this study, sponsor queries and dual entry procedures proved time and cost inefficient in detecting data discrepancies.

Conclusion: We advocate a more evidence-based approach for enhancing data integrity throughout the process of clinical data management.

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5.1   Introduction

The price of drugs has increased and consequently the pharmaceutical value chain has come under scrutiny [157]. Drug pipelines are dwindling, leading to increasing cost for drug development [158], and patients are charged more for their medications [66, 71]. Clinical phases of drug development require significant resources to assure patient safety and data integrity, the latter being endorsed by clinical data management departments (CDM) [66, 71]. In view of the high investment in clinical development, CDM could be a suitable candidate for cost savings.

Regulatory bodies have intensified administrative specifications for every process within clinical trials, aimed at preventing fraud and medical incidents [66]. These developments are principally useful but have strongly added to the operational difficulties of performing clinical trials. International Organization for Standardization and International Conference on Harmonization documents only specify that data should be accurate, complete, legible and timely [159]. With no instruction on how to attain or achieve this, trial organizers create individualized solutions.

As a result, industry dogma defines how data integrity and quality can only be guaranteed through 100% data validation. The current best practice for assuring data integrity entails several procedures at each step of the study life cycle [160], including dual-data entry, external audits, regular external and internal monitoring, monitor queries, sponsor queries and governmental audits[A]. Each audit and monitoring procedure applies similar data validation tools [161].

In this study we examined the cost and potential efficacy of commonly used methods of assuring data integrity, focusing on sponsor queries and dual data entry methodologies. We argue that the sum of all procedures are costly and labour intensive, but may be excessive as the final objective is that trial results are reliable. We find that not all individual data points have to be correct, as randomization assures absence of bias. Moreover, there seems to be no distinction between trivial and critical issues, seeing that not all data points are equally important for statistical evaluation [162]. We suggest an evidence-based approach to select actively critical parameters for assuring data integrity.

5.2   Methodology

First, we assessed the efficacy of the sponsor query procedure[B]. The study was performed at the Centre for Human Drug Research (CHDR), an academic oriented CRO with qualified personnel and clearly defined standards of operation (SOP) with an autonomous quality-assurance officer. For this analysis three phase I studies were selected, each having

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[A] The innovation of direct data entry (recording the data directly into an electronic system, eliminating the use of paper CRFs) has not been taken into account in this research.

[B] There are three types of queries based on who identified the query: CRO internal queries, monitor queries and sponsor queries. Sponsor originated queries are the only formally recorded queries that are communicated from the sponsor back to the CRO. CRO internal queries or monitor queries are usually reported by word-of-mouth or e-mail. However a full accurate report of these types of queries is not available.

similar data processing routes, but differing in sponsors, number of participating volunteers, duration and time period in which they were performed. One thousand three hundred and ninety-five sponsor queries from the three studies were reviewed.

Sponsor queries were assessed on two facets, keeping in mind that one query addresses one data point. A query was evaluated on content (scores are based on mutually exclusive categories, data point content, data point characteristic, query destination for answering, query topic and re-queries) and impact (scores are based on a five-question relative impact model, Table 5.1). All queries were scored by two arbiters in a double-blind fashion, and conflicting results were reviewed and resolved by an independent CDM consultant.

The data were analyzed using statistical descriptives, followed by Fisher-exact and Pearson's Chi-Squared to assess the relative association between categories. We studied associations between data point content parameters and the five impact questions individually, and refuted the null hypothesis each time. Second we reviewed the dual-data entry procedure. We used information on dual-entered study data as conducted at CHDR over the last 5 years in their trial database. Numerical data from first and second entry were compared and if a change was made on the second entry (assumed to indicate a discrepant first entry) the percentage difference between the two entries was recorded ignoring the positive or negative value. If a text value was changed during second entry the difference in number of characters was expressed as a percentage of the original entry. Ultimately; the cost involved was estimated based on a procedural flow-chart and real-time recording of activities at the CRO.

5.3   Results

5.3.1   *Sponsor Query Assessment*

When assessing the query content parameter, 70% of queries addressed administrative qualities of the data point, for example an unclear checked box, whereas 12% of the queries addressed a medical data point. For query impact, 80% of the queries required a confirmation of the data point. The majority of the data points queried were related to a clinical endpoint (68%). There were only six queries (0.4% from 1395 queries and 0.001% of the combined 599,154 data points) that might have influenced the results of the clinical trials if the discrepancy had not been revealed. This leads to a number needed to treat of 10,000 data points in order to find a possible significant error. The assessment was conservative as the six queries concerned a discrepancy in the coding of a non-serious adverse event. Five of the six queries were related to an administrative parameter but referred to a critical data point that could potentially influence the trial results.

The cost of the sponsor-CRO query procedure cannot be accurately defined. However, if we assume that the handling of a single query by staff at the trial site and the sponsor takes about 1 h combined, the cost can be conservatively estimated at about €150. This means that for the three trials about €200,000 was spent for the correction of a minute amount of erroneous data.

Table 5.1　　Impact of sponsor queries

Table showing impact of sponsor queries based on the five question impact measure (per cent accurate to 2 decimal places); Impact Question 1 refers to whether the data point is adjusted as a direct consequence of the query. Impact Question 2 indicates whether the query challenges the credibility of the data point, by stating 'please confirm'. Impact Question 3 refers to whether the data point queried is related to a clinical endpoint. Impact Question 4 refers to the empirical judgment of whether the data point has potential statistical impact on its specific parameter. Impact Question 5 asks; would the discrepant data, if left unnoticed by the sponsor query, have any influence on the outcome of the clinical trial? Below Impact Question 5 is a description of the six sponsor queries that could potentially influence the statistics of the clinical trial

PART A		
Question	**Frequency**	**Percent/ %**
Impact Q1: Was data changed?		
No	1003	71.90
Yes	392	28.10
Impact Q2: Was confirmation asked for a data point?		
No	199	14.27
Yes	1196	85.73
Impact Q3: Did the query concern an endpoint?		
No	298	21.39
Primary	570	40.92
Secondary	382	27.42
Other	143	10.27
Impact Q4: Was the change significant for the specific data point?		
No	1326	95.05
Yes	69	4.95
Impact Q5: Could the change have changed the results of the trial?		
No	1389	99.57
Yes	6	0.43

PART B	
Impact Q5: Explained	*Sponsor Query*
A	On the *General Physical Examination Page* a very long abnormality for psychiatric. Behaviour is recorded. This term is too long to enter on this page, therefore DE wrote a comment
B	The date and time performed should respect the theoretical time. Please verify and/or confirm
C	Actual does should be equal to planned dose. Please correct
D	First inhalation of product has a comment, indicating that a leak existed, but full actual dose is reported. Please correct or explain.
E	The estimated date is prior to the demography date. Please clarify
F	An AE even took place, and is recorded with *action taken C.O.* The corresponding CNP page is empty. Please provide treatment/procedures with relevant information to be recorded on the CNP, or verify that the action *O* can be removed for the AE.

5.3.2   The Dual Data-Entry Procedure

We evaluated the efficacy of this procedure to detect significant errors that might influence the outcome or conclusions of a trial (Table 5.2).Of the total number of dual entries (n = 1,605,682) 1.8% were changed during dual entry and the average change amounted to 156% of the primary entered original value. The magnitude of most of these changes was within 0–150%, with outliers of over 500% (Figure 5.1). The parameters tested were measured at least on 10 occasions in at least 10 studies.

Table 5.2   CHDR database inspection of single and dual entry.

The table shows the descriptive results of the data points changed after dual entry. % value is accurate to two decimal places.

	Number of data points	Percent (%)
Total number of data points	2,806,797	-
Single Entry	1,230,738	-
Dual Entry	1,576,059	-
Number changed after Single Entry	22,533	1.83
% Change	-	155.80
Number changed after Dual Entry	1242	5.50

If these changes were all in one direction this would lead to a maximum theoretical difference in the average value of a data set of 1.7% compared with the situation in which the errors were not detected. The probability of such a difference leading to an important change in statistical inference is low in view of the normal variability in biological data that generally exceeds 10%.

Dual entry of this number of data points (assuming 10 seconds per entry) approximately requires 2 man years at an all inclusive cost of approximately €200,000.

5.4   Discussion

Clinical trials are essential for evaluation of many interventions in health care making quality data indispensable. During the evolution of the pharmaceutical value chain, procedures have been added [163]. We have demonstrated that traditional procedures need to be evaluated continuously to assure that they are cost effective. By performing this evidence-based audit we have demonstrated the resources involved with generating and solving sponsor queries. Additionally, we estimated the cost savings to be considerable, excluding knock-on effects on travel expenses and infrastructure.

To reduce CDM cost we propose small procedural alterations. First direct data-entry could replace dual-data entry. Second, sponsors could review queries before blindly sending them to the CRO, filtering out queries that relate to self-evident checks. This can be accomplished through updating the trial validation plan and strategy. Third, communication between sponsor and CRO could be improved to implement a feedback

system on query type that allows for a learning curve; fewer sponsor queries nearer trial completion. Furthermore, giving more attention to the initial planning phases of a study may also affect data quality at later stages.

Last, we advocate a more evidence-based approach to clinical data management using the concept of 'resilience', the degree of flexibility for data point error. Currently there is no assessment to identify high risk data points that, if discrepant, could influence the results and consequently the conclusions drawn from a trial. We hypothesize that it is possible to pre-select these susceptible data points based on two criteria: its relation to a clinical endpoint and its flexibility for being discrepant. The latter criterion can be forecast using power-based calculations to identify high risk data points (P = 0.95 for example), that have the potential to influence the statistics if discrepant. This will reduce the resources involved as instigated by industry dogma and increase CDM efficiency.

Figure 5.1   Histogram showing magnitude of differences between first and second data entry
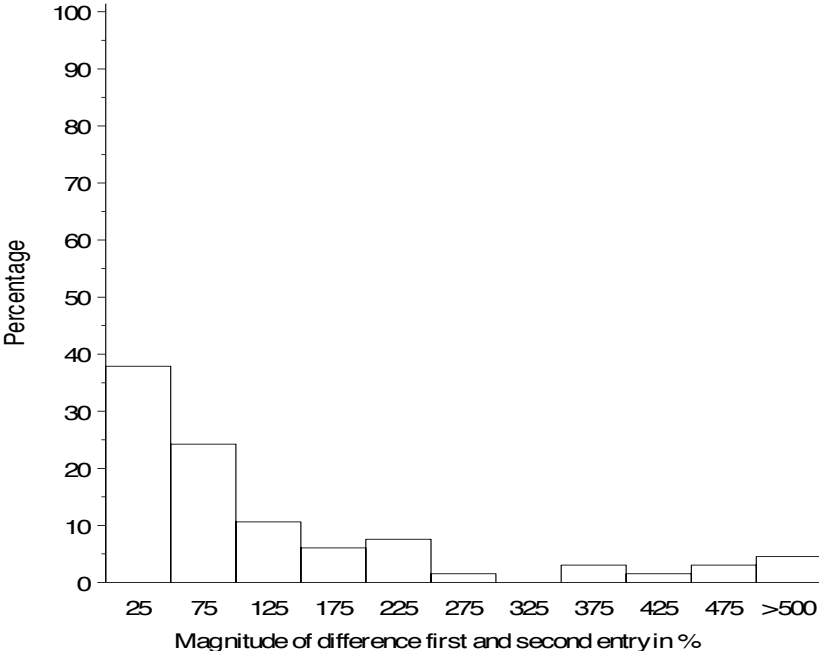
5.4.1 Considerations

Several restrictions apply to this study. First, the sample consisted of only three studies. Although selection was actively performed to prevent structural bias and spread the variables, it was only a small sample compared with the hundreds of drug trials performed on a global scale. Additionally, the extremely low detection rate of erroneous values may not be representative for other situations. They were obtained in a GCP-regulated and professionally staffed unit, making error rates (and also cost per error) quite different from other environments. The value of different quality assurance procedures therefore might be tested for that particular environment. Our data and methodology may assist with this.

This article presents the first empirical study on the topic of sponsor queries and the CDM system. This pilot study can benefit scientific organizations and pharmaceutical companies by starting to rethink the concept of data validation and current procedures to achieve this.

Chapter Six: Scratching the Surface

Exploratory Sector Level Analysis of Key Opinion Leaders on Novel Adjuvanted-Vaccine Development

Abstract
Chapter 6 offers an exploratory view on the potentially rate-limiting factors encountered during adjuvanted-vaccine development that affect value chain dynamics. Adjuvants are considered immunostimulating substances that can be added to a vaccine. Although adjuvants have the potential to elicit adverse reactions, they also offer certain benefits including; increasing the immune response in senescent population groups and dose-sparing properties. Nevertheless, after approximately 90 years of R&D, we question ourselves why only four adjuvants have been approved for use in human vaccines? Although ample literature is available describing the main risks for developing adjuvanted-vaccine candidates, it remains unclear as to how these potentially rate-limiting factors compare and interact. Key opinion leaders in the field of adjuvanted-vaccine development were approached in order to collect a unique qualitative empirical dataset

Pronker, ES
Weenen, TC
Commandeur, HR
Claassen, E
Osterhaus, ADME

6.1 Introduction

Vaccines are considered to be the most effective medical intervention in controlling the spread of infectious diseases for the benefit of public health [59]. Met with severe opposition at the start of their introduction in the 19th century [48], Edward Jenner's experiments led to the single greatest accomplishment in medical history: global eradication of smallpox by 1979[59]. Although vaccination campaigns today are still facing an anti-movement [164], the vaccine industry has fruitfully produced prophylactic and therapeutic solutions for over 25 human infectious diseases [21]. Additionally the industry is yielding blockbuster products, including Wyeth's Prevnar® and Merck's Gardasil® both reaching annual sales over US $ 1 Billion [165]. Representing a solid 2% within the pharmaceutical framework, the value of the vaccine industry is predicted to surpass the US $ 30 Billion mark by 2015 [55]. Furthermore, the vaccine industry is realizing an astounding compound annual growth rate (CAGR[A]) of 5.5%, compared to a mere 0.3% for new chemical entities (NCE) [166-168]. With such prospects, vaccines will inevitably continue to be a part of the future.

Unfortunately, since the last decade the biopharmaceutical industry has been experiencing a so-called productivity gap [169]. This concept delineates the situation whereby the proportion of consumed resources exceeds the expected turnover [170, 171]. It results in an insufficient amount of new product launches to sustain current business models and satisfy unmet medical needs [172, 173]. This phenomenon also holds true for the vaccine industry [174], mainly due to the intensifying regulatory environment, escalating research and development (R&D) costs, and improved best-standards of care [57, 99, 175]. Nevertheless, by staying innovative, vaccine manufacturers will be able to maintain their competitive niche and continue to accommodate the unmet medical needs of public health.

Vaccine R&D strategies have evolved from the basic *isolate-inactivate-inject* paradigm [176] to a multidisciplinary exercise [177]. The first generation classical vaccine antigen preparations for infectious diseases include inactivated (e.g. influenza virus) and live-attenuated methodologies (e.g. measles virus) [178-180]. However, these techniques are not feasible for all types of pathogens, creating a need for novel approaches in order to target the more complex unmet infectious diseases. Newer strategies of pathogen inactivation include more sophisticated recombinant preparations for example (e.g. Hepatitis B Virus (HBV), Human Papilloma Virus (HPV)) [179, 180]. Unfortunately, these newer methods generally do not elicit sufficiently large immune responses, making the addition of an adjuvant necessary [52, 55, 181].

Adjuvants are approved in combination with the specific vaccine antigen (Appendix A). To-date: four adjuvant compounds for use in human vaccines have received market authorization by the European competent authority, namely; Aluminium salts (Alum) in 1920, Novartis' MF59 in 1997, GlaxoSmithKline's (GSK) AS04 in 2005 and AS03 in 2008 [182]. The American Food and Drug Administration (FDA) approved two adjuvants - Alum and GSK's AS04 in 2009 [183] - and approval is currently pending for GSK AS03 [184]. Evidently, access to adjuvanted-vaccines is restricted to the regions governed by the

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[A] CAGR: Compound Annual Growth Rate, represents the period between 2009 to 2014 [166]

competent authority, making those vaccines unavailable to patients in other locations. This does not imply that these are the only adjuvant candidates or that initiatives are limited to one continent. In fact, multiple projects are ongoing at locations worldwide [52, 182, 185-192] and a compendium lists over 90 possible candidate adjuvants [193]. Nevertheless, after approximately 90 years of R&D we question ourselves why there are so few approved candidates for use in human vaccines targeting infectious diseases.

Our objective is to uncover rate-limiting factors (RLF) encountered during the adjuvanted-vaccine value chain[A] as experienced by experts in the field of adjuvant R&D. Based on the principal-agent theory (PAT), we believe a conflict of interests between the internal perceptions of key opinion leaders (KOL) on the challenges faced contribute to the low approval rate of novel adjuvant compounds. Experts interviewed represent the golden triad; knowledge institutes, industry, and regulatory and public health authorities (R/PHA)[B]. Opinions are quantified through a weighted-ranking exercise, in order to measure the variance between KOL responses. The present exploratory analysis offers previously unpublished and practical insights on the topic.

6.2   Conceptual Framework

The principal-agent theory (PAT) offers a framework for investigating opinions of KOLs on RLFs in the adjuvanted-vaccine value chain. Originating from theories on risk-sharing, PAT has evolved in the last four decades into a widely applicable and resilient socio-economic tool [194, 195]. First described by Jensen in 1976 [196], the fundamentals of PAT include a symbolic contractual relationship between two autonomous, non-competitive parties. In short; the principal delegates the agent to commit to activities, whereby the agent incurs costs in the process, in order to develop services and/or commodities on behalf of the interests of the principal. Based on this definition, the R/PHA is taken as the principal, and the KOLS representing the knowledge institutes and industry as the agents (Figure 6.1).

Nevertheless this dyadic social interaction is influenced by four main factors; information, risk, external environment and self-interest. The aspects of information asymmetry, risk management strategies (as covered by the prospect theory for example [197]) and effect of contextual factors on decision making fall beyond the scope of this discussion. Focussing on the internal preferences of each party, the system is said to experience an agency problem if these do not align. The subsequent conflicts of interests may lead the principal and the agent to adopt inaccurate beliefs, approve ineffective strategies and develop a general distrust towards each other [198]. Under these circumstances the principal can resort to increased monitoring of the agent, whereas the agent might create a demand for services against the principal's interests [199].

[A] Value chain; consists of internationally regulated R&D phases, in chronological summary; discovery, pre-clinical and toxicity screening, human clinical trials, regulatory approval and post-marketing surveillance.

[B] Knowledge institution; non-profit seeking researchers, mostly involved with discovery phases up to human clinical phase I/II of the value chain. Industry; profit-seeking companies. Regulatory/PHA; non-profit governmental and non-governmental organizations involved with regulating adjuvant R&D and market approval decisions.

Figure 6.1   Principal and agent relationships in supply-driven adjuvanted-vaccine value chain
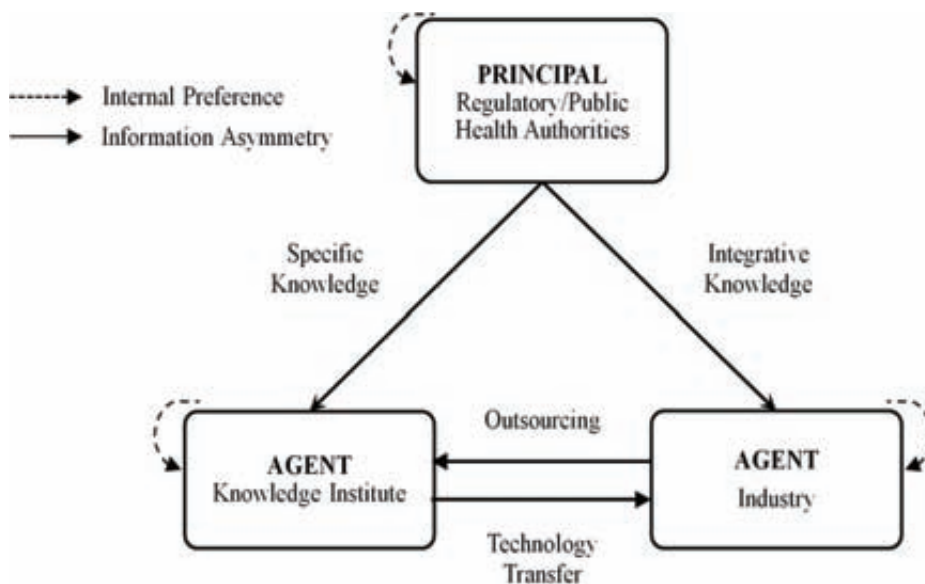
In adjuvanted-vaccine development, the principal and agents are connected in a supply-driven value chain configuration [200]. Although the industry primarily holds the burden of proof for safety, efficacy, quality and ethics, it is the interaction with the knowledge institutions and regulatory field that is required for successful adjuvanted-vaccine commercialization. As the knowledge institutes and the industry actively engage in technology and knowledge creation - specific and integrative respectively - the information asymmetry favours the agents. Moreover, information exchange from knowledge institutes to industry takes place in the form of technology transfer, and vice-versa through outsourcing [201].

In terms of self-interest, literature descriptively indicates each actor's predispositions, though limited in comparison. To start off with the principal: the R/PHA mitigate the interest of the patient population [52, 182]. Adjuvants - from the regulator's perspective - are mysterious NCEs without an EPHMRA[A] classification code. Furthermore, it remains ambiguous whether adjuvants are classified as an excipient or active compound[B]. Demonstrating their potential for inducing severe side-effects (for example Freund's Adjuvant resulting in tissue damage [185]), adjuvant compounds are considered extremely potent substances to be approached vigilantly [202]. As a result, R/PHAs have discontinued the market authorizations for vaccines, based on suggested correlation between the adjuvant compound and certain side-effects. Examples in Europe include; Berna Biotech's

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[A] EPhMRA: European Pharmaceutical Marketing Research Association for the Anatomical Classification of Pharmaceutical Products
[B] Knowledge Institute representative

NasalFlu® containing Escherigan adjuvant in 2001 due to alleged causation with Bell's palsy [203-205], Microgen's Grippol® containing polyoxidonium adjuvant due to basic allergic events in 2006 [206-209], and most recently the restricted use of GSK Pandemrix® containing AS03 adjuvant, which is pending additional research into the suspected correlation with narcolepsy in Scandinavian countries in 2010 [210].

On the other hand, the general attitude of the agents towards adjuvants is described in the literature as more favourable. Both knowledge institutes and industry acknowledge the potential of an adjuvant to enhance the immune response, even with reduced antigen concentration in the vaccine. Nevertheless, publications also highlight the drawbacks; restricted international collaboration due to a lack of suitable comparators [211] and the return-of-investment is estimated to be negligible [52, 188]. An example of a firm voluntarily revoking a market authorized adjuvanted-vaccine is Sanofi Pasteur's Humenza® containing AF03 adjuvant in 2011, due to commercial reasons [212, 213].

This research supplements the already existing body of literature with a quantitative comparison of the internal-preferences. Opinions on RLFs are considered to reflect self-interest, which is believed to be distinct for the three groups of KOLs involved in adjuvant R&D. By measuring the perceptions on RLFs, we intend to uncover proximities between the internal-preferences of each KOL. The resulting exploratory evaluation of PAT could provide novel insights for the adjuvanted-vaccine development community.

6.3   Methodology

We define RLFs as elements encountered throughout the vaccine value chain, potentially delaying procedures towards the ultimate goal of successful commercialization. Evidently, each adjuvant is developed under a unique set of circumstances, yet there are certain universal factors that influence the survival of all adjuvant projects [182, 214]. By recognizing in the literature that certain core factors occur in distinctive phases of the value chain, a framework was designed to accommodate for this (Figure 6.2; Appendix B). Validated in three pilot interview sessions prior to implementation; this framework forms the back-bone to the 60 minute semi-structured interviews[A]. Furthermore, experts were selected using the snow-ball method, allowing it to progress for three generations in order to reduce selection bias [215].

Based on the framework, KOLs were asked to complete a weighted-ranking exercise. Weighted-ranking is a tool used to quantify the opinions on a set of pre-determined elements by capturing the associations between core factors and the degree they are assessed as rate-limiting [216, 217]. It allows experts to quantitatively indicate their perceived magnitude on the influence of particular RLFs. KOLs were asked to rank their personal top-ten list of RLFs and indicate its weight by distributing 100 points over the ten factors selected. Relative weighted ranks were calculated for each RLF per respondent (x) using the formula on page 60. Subsequently the relative weighted ranks were aggregated according to the three KOL groups.

[A] Interview tool available upon request

$$RLF\ Relative\ Weighted\ Rank_x =$$

$$\left(\left(\frac{(11 - Rank_x)}{11}\right) * 100\right) * \left(\left(\frac{(Weight_x)}{\sum Top\ 10\ RLF\ Weight}\right) * 100\right)$$

The weighted and ranked top-ten list generated is headed by those factors that have the greatest influence to the continuation of the value chain. Consequently, factors ranked lower down the list remain essential to success, however are considered to have an attenuated impact on the overall outcome of the value chain. The results were supplemented by a univariate ANOVA for the statistical variance between the perceptions of each KOL group.

In order to uncover underlying reasons for the differences in opinions, interview transcripts are analyzed according to the grounded theory [218]. Open-axial coding was completed by three researchers in double-blind design, employing Atlas.ti software © [219]. The resulting axial-codes were organized into a visual network by linking associations between the phenomena. This overview allows for the identification of key concepts that offer explanations for the different self-interests between the principal and agents.

Figure 6.2   Value Chain Framework (c) RLFs categorized according to their sphere of influence [142, 172, 182, 214, 220, 221].

Reg.	Regulatory approval of the adjuvanted-vaccine
RLF	Rate limiting factor
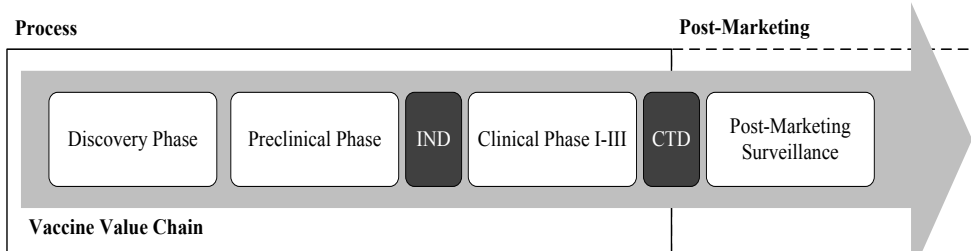
Process RLF	Post-Marketing RLF
Biomarkers	Commercial
Communication	Education
Cost of Goods and Upscaling	Liability
Efficacy	Post-Marketing Surveillance
Regulations	Price
Feasibility	Reimbursement
Formulatability	
Intellectual Property	
Quality	
Safety	

6.4   Results and Analysis

27 KOLs voluntarily participated[A], of which 6 represent the knowledge institutions[B], 12 the industry[C] and 9 are R/PHA officials[D]. To start off with, KOLs were prompted with the framework and invited to comment on the list of potentially RLFs as well as their location within the framework. Saturation is achieved soon after the pilot interviews (Figure 6.3). Only respondent 18 - of R/PHA origin - introduced a novel factor of vaccine administration. Nevertheless, the magnitude for this additional factor is not perceived as significant enough by other experts to appear in the final outcome of the weighted ranking exercise. It is therefore assumed the framework reflects the 20 most important potential RLFs for novel adjuvant R&D according to the KOLs.

Figure 6.3   Saturation curves of the rate-limiting factors in the framework.
Blank markers[E] indicate respondents unable to complete the weighted ranking

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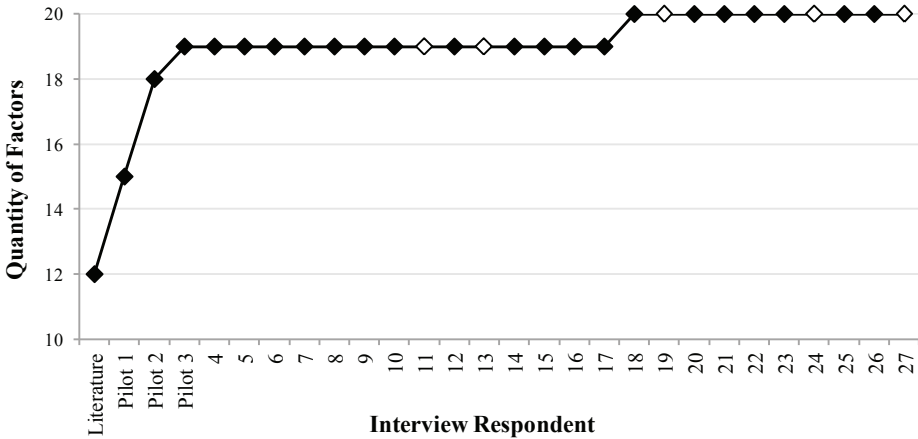
[A] All interviews are completed within a period of 4 months to ensure consistency of interview technique

[B] Knowledge Institutions represented by; Vrije Universiteit Amsterdam, the Netherlands; Erasmus University Rotterdam, The Netherlands; Glasgow University, United Kingdom; University of Groningen, The Netherlands; University of Lausanne, Switzerland.

[C] Industry represented by; Litevax BV; Intervet/Schering-Plough Animal Health and Intervet International; Abbott Biologicals BV; Brenntag-Nordic; Novartis Vaccines & Diagnostics; Merck; Crucell BV; CSL Limited; GSK Biologics; Sanofi Pasteur; Biomedical Primate research centre, the Netherlands; Staten Serum Institute, Denmark

[D] Regulatory/ PHA represented by; European Commission; European Vaccine Initiative; European Adjuvant Advisory Committee; Medical Ethics Board the Netherlands; Ministry of Public Health Belgium (FAGG); Ministry Public Health the Netherlands (RIVM/NVI)

[E] Non-respondents are equally distributed amongst the three KOL groups; 1 representing the Knowledge Institute, 1 representing the R/PHA, and 3 representing the Industry.

6.4.1   Weighted Ranking

Results indicate a significant internal validity of KOL group responses (Figure 6.4). Additionally, the ANOVA analysis revealed no significant effect between the weighted ranking values and KOL group membership (Table 6.1). However, the weighted ranking responses are significantly dependent on the RLF itself.

Figure 6.4   Weighted-ranking, ordered according to all results. Standard deviations indicated.

PMS	Post Marketing Surveillance
CoG	Cost of goods and up scaling
R/PHA	Regulatory and Public Health Authority
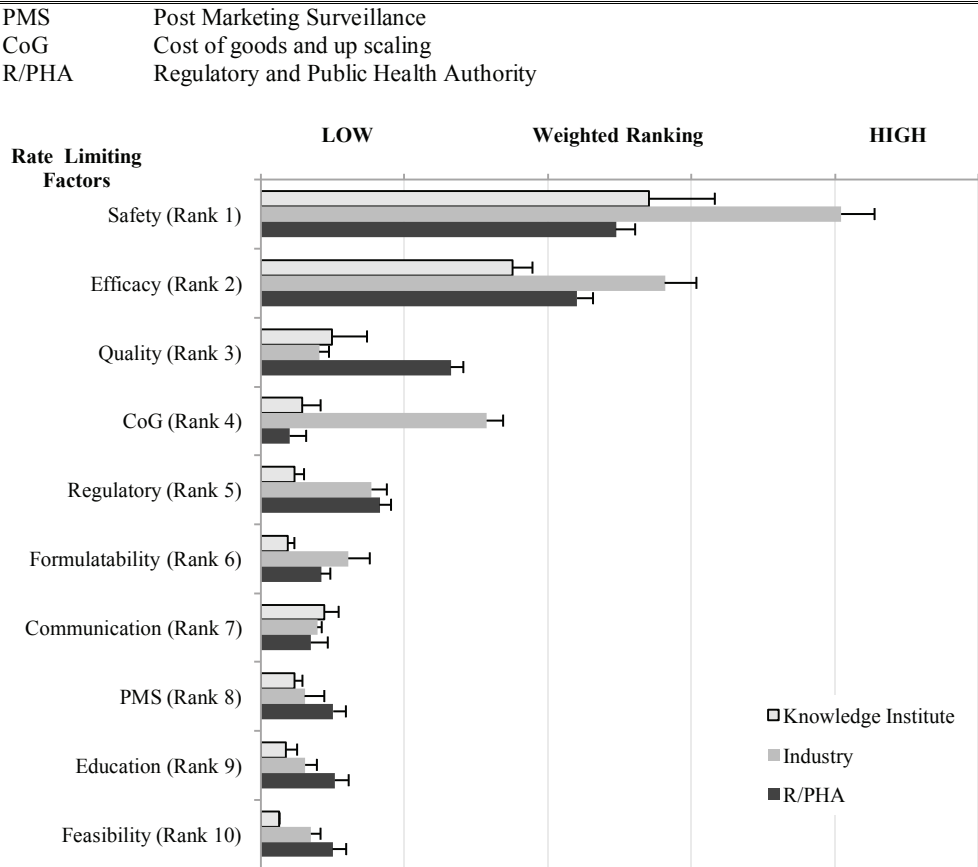
By mapping the factors in a decision matrix configuration, similarities and difference between KOL responses are visualized (Figure 6.5). The top-ten of the principal's opinion is taken as a reference, to which the responses of the agents are compared. Starting with the similarities; all KOLs unanimously position safety and efficacy in first and second place respectively. Differences in opinions are evident from the third position onwards, of which quality, regulatory, cost of goods (CoG), intellectual property (IP) and commercial RLFs are selected for further clarification.

6.4.1.1 Safety

Safety has a dichotomous impact on the value chain. As one expert summarizes; "At the end of the day, we need to separate safety from the image of safety[A]." Indeed, many KOLs are confronted by the prejudice that adjuvants in a vaccine system imply safety concerns[B], when it is rarely the determining factor that would stop adjuvanted-vaccine development[C]. Safety, by itself, refers to the actual indicators of the item, whereas the image of safety deals with the interpretation of the data.

Establishing safety takes place at every stage of the value chain. It is an assessment of the physical side-effects from administering the adjuvanted-vaccine, and forecasting the probability of developing the predicted acute and/or chronic manifestations. Measuring safety is a meticulous exercise, whereby the outcome is dependent on the antigen-adjuvant combination and related to the animal model. Moreover, results of the preclinical phase are not predictive for the effect in human clinical trials, which in turn does not project adverse reactions in the post-marketing phase. Consequently, establishing causality between the side-effects and the various components of the vaccine-complex remains challenging.

The second aspect - implicating the interpretation of the safety data - is usually accomplished using a risk-benefit ratio. Determining the thresholds within which the risk of developing certain side effects are tolerated against the benefits of administering the prophylactic vaccine versus an alternative intervention is an arbitrary task, specific to each class of KOL. The perception is influenced by; the current standard of treatment, scale of the disease burden, severity of disease pathogenesis, demographics of the target population and whether the vaccine is prophylactic or therapeutic. Interviews reveal that each class of KOL is unaware of the limits set by the other groups, although the image of safety is decisive in the current market space[D]. As a result, safety is regarded by all KOLs as the least resilient of the rate-limiting factors, with potentially the largest impact on the continuation of adjuvant R&D.

6.4.1.2 Efficacy

Efficacy is the second highest rated factor. In a purely practical sense, an effective adjuvant can be developed without it being safe - whether it will be included in a vaccine is something else[E]. Additionally, there is also no point in continuing development if the adjuvant is not effective: "There are a couple of cases where this happened, but eventually you will have to own up[F]." Efficacy data justifies the inclusion of the adjuvant in the vaccine, and it can best be divided into protective efficacy and immunogenicity[G].

[A] Knowledge Institute representative

[B] Regulator and PHA representative

[C] Knowledge Institute representative

[D] Industry representative

[E] Industry representative

[F] Industry representative

[G] Regulator and PHA representative

Protective efficacy describes the complete clearance of the pathogen and the ability of the adjuvanted-vaccine to prevent disease latency. In the clinical setting, protective efficacy can be established by comparing the adjuvanted-vaccine with the current best practice in healthcare, demonstrating either non-inferiority or superiority. Nevertheless, efficacy can't always be measured accurately during clinical development. Several interview respondents believe that protective efficacy within a population is best established once the adjuvanted-vaccine has been brought onto the market[A].

Immunogenicity expresses whether the adjuvanted-vaccine has immunogenic properties. A measure for this aspect of efficacy includes the correlate of protection, which is a physical indication of the individual's immune response [222]. In general; infectious diseases for which vaccines are currently available have established correlates of protection. For example seasonal influenza vaccines, whereby target levels of antibody titres are predictive for sero- and clinical-protection [223]. Most other diseases do not have accepted correlates of protection, such as HIV/AIDS for example [224]. In the case of the latter scenario, a situation is created whereby multiple working definitions of immunogenicity for the same infectious disease co-exist. Combined with the sentiment research teams hold for their own projects, it contributes to the general conviction that "one man's adjuvant is another's accident waiting to happen[B]." It evokes a cautious attitude during the development of an adjuvanted-vaccine. All reasons combined; this factor is considered to have low threshold beyond which it will be interpreted as rate-limiting.

Table 6.1   ANOVA results

PMS   Post Marketing Surveillance

Ranking order Principal	Source	df	F	Sig. p-value
1	Safety	2	.700	.509
2	Efficacy	2	.263	.771
3	Quality	2	1.649	.236
4	Regulatory	2	.965	.414
5	Education	2	.559	.595
6	PMS	2	.210	.816
7	Feasibility	2	1.400	.346
8	Formulatability	2	.455	.658
9	Liability	1	N.A.	N.A.
10	Communication	2	,724	.514
-	RLF	10	8.378	.000
-	KOL group	2	.145	.865
-	KOL group * RLF	20	.513	.956

[A] Industry representative

[B] Knowledge Institute representative

6.4.1.3   Quality

Quality is prioritized in third place by both the knowledge institute and R/PHA KOLs and in eighth place by industry representatives. From the perspective of the knowledge institutes, quality is experienced as a rate limiting factor specifically during valorization activities. Most academic research environments do not match the stringently regulated industrial setting. Quality is therefore experienced as limiting technology transfer opportunities[A].

The R/PHA representatives are also of the opinion that quality is imperative at every stage of the value chain, equating it with safety. Quality is multi-disciplinary, and includes monitoring different R&D aspects, including but not limited to; quality of ingredients, batch consistency and data management. As quality relates to essentially all R&D activities, it permits low margins for error.

As described by experts representing the industry, quality is an essential aspect in adjuvant R&D but it is not necessarily a high ranking RLF. Quality is viewed as inherent to the process of adjuvant R&D, since product development requires compliance with good manufacturing practices and other legislations[B]. It is a secondary effect that could turn quality into a rate-limiting factor, namely the considerable cost associated with it. Consequently this is reflected in the results, as Industry KOLs have ranked CoG in third place (Section 6.4.1.5).

6.4.1.4   Regulatory

Any argument relating to the regulatory environment as a RLF comes in at fourth position for both the R/PHA and industry KOLs. Adjuvanted-vaccine development is regulated at national, international and global (ICH[C]/ISO[D]) levels, through hard[E] and soft[F] legislature. According to both agents, the regulations are often experienced as suggestive. Nevertheless, the R/PHAs attempt to create a balance between formulating generalized legislation that is too difficult to comply with, and passing lenient measures that would automatically approve adjuvant compounds without R/PHA consent[G].

From the perspective of the industry KOLs, there are two main reasons for the high weighted-rank. First, an adjuvant is never approved for market entry as a single entity but as a component in the vaccine system. Nevertheless, novel adjuvant compounds

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[A] Knowledge Institute representative

[B] Industry representative

[C] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

[D] International Organization for Standardization (ISO)

[E] Hard regulations include completing certain documents in the adjuvanted-vaccine dossier, for example

[F] Soft regulations offer guidance to the interpretation of the hard regulations

[G] Industry representative

considered for inclusion require sufficient proof of safety, efficacy and quality[A]. Especially with novel adjuvant innovations, the assessment concerning sufficient proof by the R/PHA officials remains unclear to industry representatives[B].

Second; the financial consequences for some of the R/PHA inquiries concerning the ajduvanted-vaccine dossier. For example when the R/PHA official alludes to the correlation between the adjuvanted-vaccine and the probability of developing an auto-immune disease. In principal this is a purely theoretical concept, as the cause for most auto-immune diseases remains unknown[C]. Due to experimental practicalities, the only remaining option for the manufacturer would be to monitor the adjuvanted-vaccine closely in resource intensive, long-term observational studies. Depending on the sponsor, R&D activities could be suspended following this R/PHA decision.

Figure 6.5   **Matrix showing top-10 rate-limiting factors. The order generated by the principal (R/PHA) is taken as a reference, to which the behaviour of the curves representing the agents' internal preference is compared.**

PMS   Post Marketing Surveillance
R/PHA   Regulatory and Public Health Authority
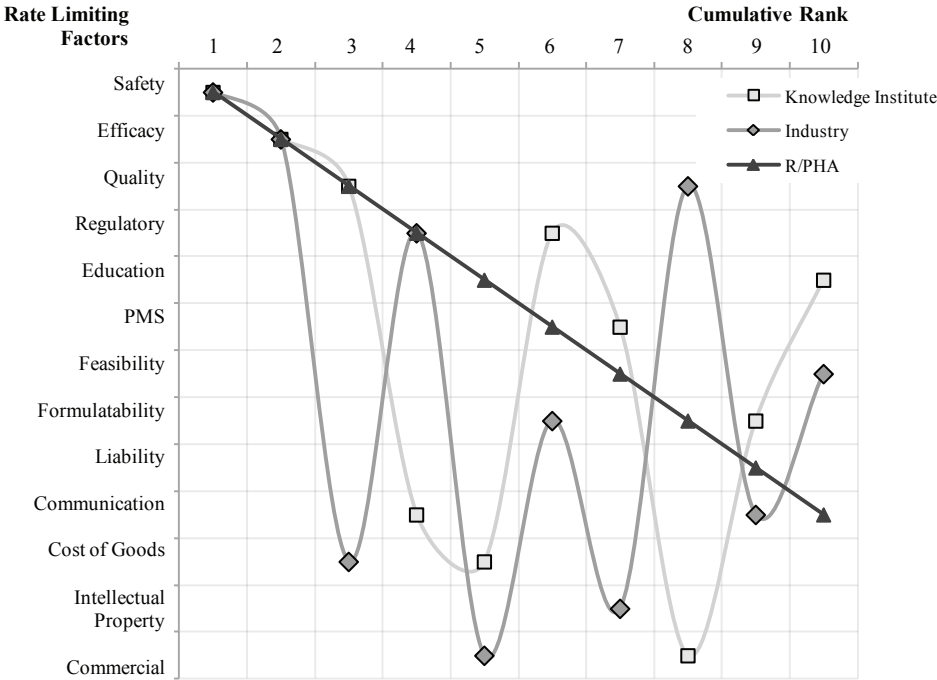
[A] Regulator and PHA representative

[B] Industry representative

[C] Knowledge institute representative

6.4.1.5 Cost of Goods and Up Scaling

The cost of goods and up scaling is considered by the R/PHA KOLs as insignificant. In fact, all interviewees agree that the R/PHA should remain blind to this aspect in order to maintain their focus on assessing health benefits. However, the R/PHA advocate that if knowledge and technology on up-scaling is available, to include it in the dossier at the earliest possible development stage. Ranking at fifth place, the knowledge institute KOLs realize the financial context of adjuvant development and envision this as a practical RLF. For the industry KOLs, this RLF is ranked in third place and is closely associated with feasibility. Up scaling is considered a part of the business case and should result in the final adjuvanted-vaccine product to enter the market at a competitive price.

6.4.1.6 Intellectual Property

To the industry KOLs, intellectual property (IP) is perceived as significant enough to rank in 7th place. For the industry representatives patents are seen as an inevitable commodity, essential in advancing product development. Nevertheless, specific unpatentable in-house knowledge is required for manufacturing the adjuvant; "I can give you all the ingredients for an apple-pie, but we would both make two completely different cakes[A]." In fact, patents are only considered to be rate-limiting if the vaccine requires the patented adjuvant from a third party and the license is unattainable.

Both R/PHA and knowledge institute representatives are aware of the necessity for IP protection in advancing commercial activities. Even though R/PHA officials are not involved with IP, an increasing number of knowledge institutes have established technology transfer offices and stimulate patent application. Nevertheless, it is highly unusual for a product to be developed beyond the pre-clinical stages by a university. In the knowledge institute setting, the patent itself is often regarded as the final product[B].

6.4.1.7 Commercial

Commercial relates to the channels required for distributing the adjuvanted-vaccine to the end consumer. For the industry representatives in particular, the commercial element is taken into consideration prior to developing the adjuvanted-vaccine. For example; designing a product for the economically developing countries where the access to cold-chain and last-mile logistics could influence R&D strategies. Most interviewed KOLs also recognize the significance of pre-existing public and private distribution channels, and the possibilities for creating a new channel if it is not available.

6.4.2 Self-Interest

The 27 interview transcripts were analyzed in order to gain insight into the underlying social constructs influencing KOL self-interest. By applying the grounded theory, the

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[A] Industry representative

[B] Knowledge Institute representative

content analysis resulted in 1118 open codes which were subsequently categorized into 57 axial codes. Through linking the main associations and directional relationships between the axial codes, an overview is created revealing the main social constructs (Figure 6.6). As derived from the interviews, the foundation for the KOLs' perspective on adjuvanted-vaccines encompasses four main concepts; risk management, innovation strategy, valuation and funding.

6.4.2.1　　　　*Risk Management*

Although falling beyond the scope of this analysis, risk management strategies essentially influence the internal-preferences of the KOLs on adjuvanted-vaccines. The interview analysis reflects several items that could influence the perception of risk, including; historical precedents (e.g. track record, collective memory), culture (e.g. bias for success, corporate culture, perception of failure) and advocacy between actors (e.g. networking and social strategy). Especially actor advocacy and the relationship dynamics between the main actors seem to be influenced by the social construct of responsibility[A]. With regard to the perceived risk for developing and commercializing an adjuvanted-vaccine, responsibility stimulates the discussion concerning the proportional allocation of reward and liability between the actors. Risk management affects, and is simultaneously affected by, innovation strategies and funding.

6.4.2.2　　　　*Innovation Strategy*

In the pharmaceutical market, economic growth is generally based on incremental innovation, although radical innovations are considered more valuable [225]. Nevertheless, as described by most KOLS, the caveat with radical innovation is the barrier to the social recognition and acceptance of novelties [226]. The figure lists various items specific to adjuvanted-vaccine development for which social acceptance and recognition are challenged. Ultimately, the perception of each KOL on the value of innovations forms the basis to innovation strategies, which in turn influences risk management decisions.

6.4.2.3　　　　*Valuation*

Valuation is broadly defined to encompass individual-, organizational- and societal-level perception on the benefit of the adjuvanted-vaccine in both economic and social values. Essentially it is the valuation process that fuels the conflict-of-interest between the principal and agents. Based on the interview transcripts, the perceived value of an adjuvanted-vaccine is influenced by; contextual factors, epidemiological data, the value chain and the market landscape. Consequently, each KOL group has their own interpretation of those four features, which leads to different conclusions regarding the priority for adjuvanted-vaccine R&D projects. As a result of the different agendas, the agents might not target an infectious disease area as prioritized by the principal. This leads to the creation of specific tax-breaks or subsidies in order to financially stimulate the agents in a certain R&D direction.

[A] Responsibility is viewed in terms of reward and liability

6.4.2.4   *Funding*

This final pillar is the financial reflection on KOL valuation and risk management perspectives associated with adjuvanted-vaccine R&D. Funding entails a practical assessment of the income (for example investment from altruistic foundations), the operational costs (for example CoG) and return-on-investment (for example willingness-to-pay). According to the majority of KOLs, the cost for the adjuvant R&D can only be recovered after significant timelines.

Figure 6.6   Grounded Theory system analysis of the axial codes
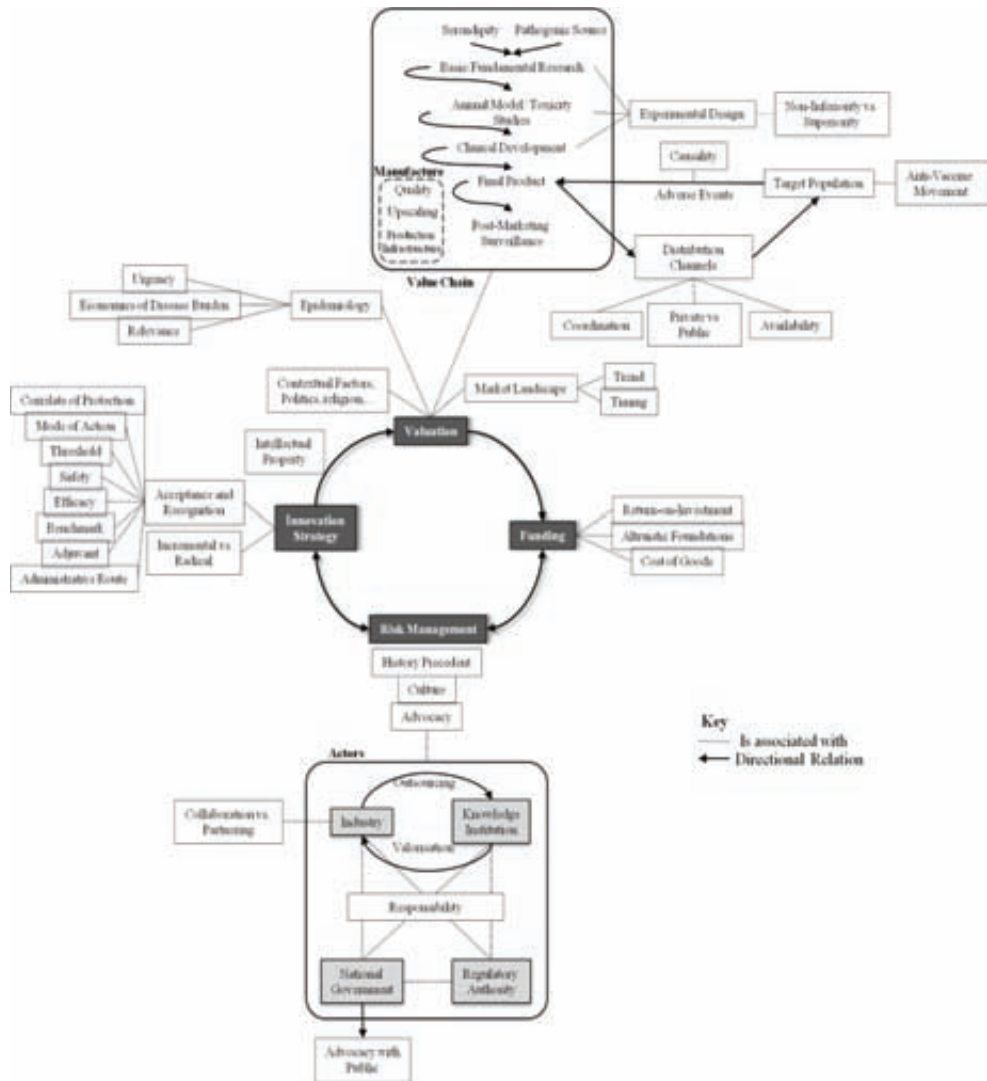
6.5   Discussion

In the view that global society is threatened by numerous unmet medical needs that require appropriate prophylactic vaccination campaigns, innovative solutions are sought in order to address those pressing issues. Such measures include, but are not limited to, adjuvants. Adjuvants prove indispensible in the future of effective human vaccine development, yet add a degree of uncertainty to the already risk intensive vaccine value chain. Additionally, the benefits for including adjuvant compounds in a vaccine outweigh the opposing arguments.

This exploratory study merely uncovers the tip-of-the iceberg when it comes to revealing the challenges faced during adjuvanted-vaccine development. The data presents a snap-shot of the current situation by quantitatively comparing opinions of experts active within the field of adjuvant R&D. Nevertheless, several KOLs were unable to complete the exercise. The main argument is related to the interconnectedness of the factors, whereby any issue regarding a particular RLF could produce a knock-on effect throughout the value chain. In other words; all RLFs are equally important for the outcome of the whole process. Indeed the framework presents an over-simplified version of the value chain, revealing only the core RLFs. For the purpose of this exploratory study, the framework attains it's goal in providing a validated starting point for further research into the topic.

Additionally, plotting the weighted-ranking results in a matrix configuration proves a valuable method for measuring the internal-preference component of PAT and subsequently visualizing the similarities and differences. Based on the internal-preferences, adjuvant R&D is diagnosed with a partial agency problem. Partial in the sense that on the one hand the weighted-ranking data reflecting the KOLs internal preference only overlaps with regard to two RLFs. The remaining RLFs indicate the topics which potentially fuel the conflict-of-interests. On the other hand, several adjuvanted-vaccines have recently been awarded market entry by the European competent authorities. Although the topics contributing to the conflicts-of-interest between the internal-preferences of the principal and agents have been identified, a comprehensive understanding of the agency-problem entails further research into the knowledge symmetry, risk and external environment.

Content analysis of the interview transcripts reveals four interlinked social constructs that could clarify the conflicting internal-preferences. Namely attitudes towards risk management, innovation strategy, valuation and funding are found to cause the differences. In the view that perceiving a factor as rate-limiting is largely depended on the self-interest of the KOL, further research on the topic of social constructs is suggested. Such data could have practical implications for promoting consensus between the KOLs regarding critical RLFs, as well as determining the resiliency on the corresponding acceptable thresholds.

This study was designed to explore the topic of rate-limiting factors, and not intended to solve the issues encountered during adjuvanted-vaccine development. In light of the observations, we would question whether a universal order of RLFs can be attained, and whether this will facilitate successful commercialization of novel adjuvanted-vaccines in the future. Moreover, in the view that the majority of vaccine candidates never attain

market registration [172, 174], we would advocate more transparency on reasons for project discontinuation. At the end of the day; sharing lessons learned from failed attempts could prove valuable for advancing the field of vaccinology, in order to win the infectious disease battle for the benefit of public health.

6.6   Appendix A

Depending on the infectious pathogen and the preparation technique some antigens are not immunogenic enough, which is when adding an adjuvant to the vaccine complex is beneficial [227]. The term adjuvant is derived from the latin word for help - adjuvare [52]. It embodies the functionality of the adjuvant compounds: substances that guide the immune system more efficiently, either through a slow-release depot mechanism or facilitating antigen recognition [192].

As a science, it is based on the observation that certain substances exasperate the immune system [228-230]. This inherent immunomodulating attribute creates a catch-22 situation: it is what makes the adjuvants potent, but is simultaneously the property that causes the (serious) adverse reactions [231]. Furthermore, the precise mode of action (MOA) for various adjuvants is not fully understood [232], and they react differently dependent on the antigen and host combination. It remains an arbitrary task to design a classification system for adjuvants[A], namely due to the unique immunogenic profiles [229].

Adjuvants do not have a suitable comparator - or gold standard - for determining safety and efficacy [202, 233]. The most effective method of establishing safety and efficacy profiles is to compare the adjuvanted vaccine with a non-adjuvanted and/or alternatively adjuvanted vaccine in a randomized, double-blind, human clinical trial [221]. Adjuvant developers have yet to come across the Holy Grail – a universally applicable adjuvant that does not have any side effects. Even so, the benefits outweigh the risks and adjuvants have become an integral part to the vaccine R&D scene (Table 6.2).

[A] Attempts at categorizing include; origin of adjuvant, MOA, physiochemical properties, and administration route[52]

Table 6.2   The advantages of using adjuvants outweigh the disadvantages

Advantage	Disadvantage

• **Adjuvants support advances in vaccinology**[229]
   ○ Can support the efficacy of different routes of administration
   ○ Can support the effectiveness of needle-free devices
   ○ Can stabilize epitope conformation
   ○ Increases potency of weak peptides
 • **Adjuvants reduce the amount of antigen concentration per vaccine dose** [52, 229, 234]
   ○ Could improve safety of the vaccine, due to less antigen being administered
   ○ Reduces the likelihood of antigen competition in combination vaccines
 • **Adjuvants improve the immunogenicity of the vaccine** [55, 182, 229, 235]
   ○ (Some) generate a depot at the site of inoculation for slow release of antigen
   ○ Enhancing the speed and vigour of immune response
   ○ Accelerate the generation of a robust immune response
   ○ Prolonging the duration of the response due to memory cells
   ○ Increases the breadth of the immune response, also known as heterologous activity
   ○ Achieve qualitative alteration of the immune response
   ○ Targets Antigen-Presenting cells
   ○ Stimulates antigen uptake on Major Histocompatibility Complex class I or II
   ○ Increases antibody titres
 • **Adjuvants can improve the immune response to a vaccine in the general population** [52, 55, 182, 236] ^A
   ○ Can overcome the limited immune response in subgroups of the population, for example risk groups^A
   ○ Can potentially overcome immune tolerance
	• **Tolerability profile of short and long-term adverse events/ side-effects** [185, 229, 237]
	   ○ Local
	   ○ Systemic
	   ○ Allergic; hypersensitivity
	   ○ Disease associated events
	   ○ Auto-immunity
	   ○ Teratogenesis or abortogenesis
	   ○ Carcinogenesis
	 • **Production and Manufacturing** [55, 182, 229]
	   ○ The high cost of some modern adjuvants may offset the savings realized by the reduced antigen requirement, thereby paradoxically increasing the total cost of the product
	   ○ Complex formulation of adjuvant-antigen
	   ○ Stability issues
	   ○ Ph issues
	   ○ Reproducibility
	   ○ Upscaling
	   ○ Raw materials are expensive and could come from a source for which the quality and purity are unknown
	 • **Mechanism of action is relatively unknown** [182, 229]
	   ○ Most adjuvants have complex and multifactorial mechanisms that are often poorly understood
	   ○ High reactogenicity may result in low vaccine uptake
	 • **Environmental issues** [229]
	   ○ Spread of live vectored vaccine into the environment has unknown consequences

^A Vaccine risk groups are population groups at higher risk of infection, including newborns (immunologically immature), elderly (immunosenescent) individuals and immunocompromised patients[229]

6.7 Appendix B

Definitions of the framework categories

Code	Definition
Regulatory	Any argument relating to the regulations or regulator during the development of the adjuvanted-vaccine candidate
Communication	Any argument relating to the communication between the developer – the knowledge institute and the industry – and the regulator/PHA
Discovery phase	Referring to *in silico* and *in vitro* procedures - as factor during novel adjuvant R&D.
Pre-Clinical phase	Referring to *in vivo* studies, toxicity studies and MOA procedures - as factor during novel adjuvant R&D.
Clinical Phase	Referring to human clinical trials - as factor during novel adjuvant R&D.
Registration	Referring to the dossier of vaccine candidate being submitted to the regulator for review to attain market entry - as factor during novel adjuvant R&D.
Post-marketing Surveillance	Referring to any activities of surveillance and monitoring after the regulatory approval of the vaccine candidate into the market, as factor in novel adjuvant R&D.
Safety	Any argument relating to the safety aspect of drug delivery and drug interaction with the host as a factor in novel adjuvant R&D.
Efficacy	Any argument relating to the efficacy aspect of the compound as a factor in novel adjuvant R&D.
Quality	Any argument relating to the quality of the product, including purity of samples and other ingredients as a factor in novel adjuvant R&D.
Cost of Goods	Any argument relating to the cost of goods, where goods refer to any physical part of the final product, as a factor in novel adjuvant R&D.
Feasibility	Any argument relating to the practical feasibility of developing the novel adjuvant
Formulatability	Arguments based the composition of the vaccine, including dosage levels and ratio of ingredients, as a factor in novel adjuvant R&D.
Biomarker	Any argument relating to practical aspect of measuring safety, efficacy and quality through biomarkers, as factor in novel adjuvant R&D.
Intellectual Property	Any argument relating to the intellectual property protection as a factor in novel adjuvant R&D.
Liability	Any argument relating to the zero-tolerance policy and liability/insurance issues due to the use of the adjuvanted vaccine candidate
Price	Any argument relating to the market/sale price of the adjuvanted vaccine candidate
Commercial	Any argument relating to the production and distribution channels of the product, including logistics and up-scaling manufacturing processes
Education	Any argument representing social climate, public opinion and how the public is educated and approached after the vaccine has been approved for market entry
Reimbursement	Any argument relating reimbursement, tiered pricing and dual-pricing systems after the vaccine product has been approved for market entry
" …"	Any other argument = miscellaneous

Chapter Seven: Recipe for success?

Development of a New Generation Influenza Vaccines

Abstract
As infectious diseases cause approximately 25% of the annual global mortality, vaccines are found to be a time proven and promising response to infectious disease need. However, like for pharmaceutical small molecules, vaccine development is lengthy, risky and resource demanding. Faced with an attrition rate estimated around 80%, key opinion leaders were interviewed with the question: is there a recipe for success?

Pronker, ES
Claassen, E
Osterhaus, ADME

7.1 Introduction

"It is better to prevent disease, than to allow avoidable human suffering [2]."

The development of prophylactic vaccines targeting neglected viral infectious diseases is an unmet medical need within an international political setting. From the 57 million annual deaths worldwide, approximately 25% is attributable to infectious diseases. Of these 14.5 million, at least 8% could have been prevented by childhood vaccination [33, 238]. Although considerable progress has been made in the research and development (R&D) of vaccines, even now many existing, re-emerging and emerging infections do not have an efficient preventive moiety or vaccine.

Vaccine development is a high risk and resource intensive multidisciplinary venture. Through an internationally regulated series of phases, a safe, effective, high quality and ethical vaccine is produced. This vaccine value chain[A] takes on average 10 years requiring an estimated investment of US$ 500 million [239]. Nevertheless, developers are facing various obstacles leading to high project attrition rates [99]. The success rate of a project is greatly enhanced by collaboration between the triple helix; knowledge institutes/universities, industry and regulatory and public health authorities (R-PHA). We interviewed key opinion leaders representing these arenas with the question: is there a recipe for success?

7.2 Productivity Rates

Vaccines are believed to be the most cost-effective medical intervention for mitigating influenza infections [94, 240]. During a typical seasonal influenza outbreak, 5–20% of the population can be infected and a substantial number of patients stay at home for an average of 3–5 days. In financial terms, the annual burden in the United States of America alone is US$ 87 billion [241]. In case of a pandemic, the financial ramifications would be far greater. By introducing an efficient public campaign, combining antiviral therapies and prophylactic vaccination, this socio-economic impact can be significantly reduced.

Unfortunately, the vaccine industry is experiencing a so-called productivity gap [76]. Since the last decade a trend has been observed that resources consumed during R&D do not result in the anticipated number of product launches [77]. One aspect of this phenomenon is the success rate: the probability a candidate will successfully transition through the value chain phases [125]. When taking pre-clinical development as a starting point, approximately 6% of the vaccine candidates reach regulatory approval (Chapter 4). By comparison, inter-pandemic influenza vaccines are considered lucrative, attaining an estimated 10% success rate (Chapter 4).

[A] Value chain is internationally regulated phases a drug and vaccine have to complete before market entry. The chronological order of phases include: discovery phase, pre-clinical phase, human clinical trials phase I, II and III, regulatory approval by competent authorities, and market entry. After market entry some products need market surveillance and this phase is also known as clinical trial phase four.

This leaves the remaining 80% plus vaccine projects that will never reach the market. Initiatives may be discontinued at any point during the value chain, for any number of reasons [142, 220]. From the perspective of the entrepreneur and investor, this can be a healthy decision when taken as early as possible. It is during the initial development stages that resources invested are still relatively low. Furthermore with every completed phase; the value of a project increases while the risk is reduced [242].

7.3   Recipe for Success?

In an attempt to understand the high levels of vaccine project attrition, we approached 27 experts on their opinions of the topic[A]. 6 represent the knowledge institutions, 14 the industry and 7 are employed by the R-PHAs (Chapter 6). The interview transcripts were open-axial coded according to the grounded theory [218], resulting in a system analysis from we distilled the following four lessons for start-up companies. In random order:

7.3.1   Plan Ahead

Although seemingly a logical and cliché ingredient, experts claim it is undesirably taken for granted. By default, start-up companies focus on specific early phases in R&D, disregarding the perspective of the entire value chain. Key elements to take into consideration include project-team characteristics, and potential partnerships. The latter could guarantee clinical phase-3 entrance and huge investments in competition with 'in house products', further down the value chain.

Starting with the composition of the project team; one has to take into account the natural setting in which vaccines are developed. The multidisciplinary character requires a flexible team of experienced professionals, capable of adapting to the dynamic nature of the project. According to the experts it takes the right combination optimistic individuals to overcome the obstacles, but also control and criticism (pessimists) leading to objective decisions on project continuation. Start-up companies have the tendency to develop an emotional bond with their project, clouding realistic judgment. Perhaps larger corporations are at an advantage in this respect. Vaccine candidates are "thrown over the wall" to other departments, facilitating these decisions throughout R&D.

Second, planning ahead also pertains to considering collaborating with public and private stakeholders. According to the R-PHA representatives, the majority of start-up firms still seek regulatory advice and guidance too late. For example; scheduling the first consultation when planning to initiate human clinical trial phase I, yet returning from the meeting with protocol amendments for pre-clinical development. As a result, the experimental design has to be re-written and repeated, causing delays in the development time-line. Communication with the right stakeholders in the early stages of development greatly increases the chances of success.

[A] Interview tool available on request. Methodology and justification are described in: Chapter 6

7.3.2   *Keep it Simple*

Most re-emerging and emerging infectious diseases are not eligible for traditional whole-cell or live-attenuated inactivation strategies [176, 178]. Vaccines targeting these pathogens require novel solutions, for example; sub-unit preparations in combination with an adjuvant for sufficient immunogenicity [52, 55, 243]. Such radical innovations come at a price: developing vaccines with known correlates of protection (incremental innovations) significantly improves success rates and financial gains (Figure 7.1) [244].

Figure 7.1   Risk profile for vaccine development,

Comparing the development trends for vaccines targeting infectious disease with known correlated of protection, compared to unknown correlates of protection. The "all data" curve is labelled, yet labels apply to the other curves as well. Data is based on methodology as described in: (unpublished work) Pronker, ES. Weenen, TC. Commandeur, HR. Claassen, E. Osterhaus, ADME. September 2011. Risk in vaccine R&D quantified: considerations for Investors. Paper presented at: The Fourth ESWI Influenza Conference, Malta.

PC   pre-clinical development
PI   clinical trials phase I
PII   clinical trials phase II
PIII   clinical trials phase III
Reg.   registration with the regulatory authorities
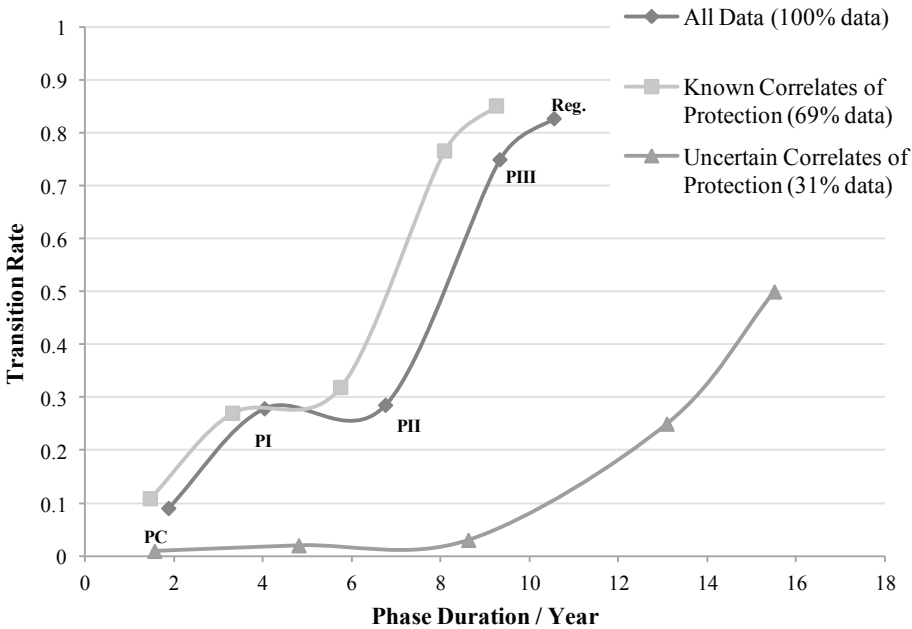
Experts also relate this lesson to up-scaling of production. Most start-up companies are involved in the discovery phase up to human clinical trials phase I or II. In these stages relatively few dosages of the vaccine candidate are validated. However, as the candidate progresses through the value chain, the necessary amounts increase exponentially. By keeping production methods straight-forward, up-scaling and down-stream-processing of the vaccine is facilitated.

7.3.3 Valuate Relevance

Experts believe that start-up firms could reduce the chances of project attrition already at the start: selecting relevant target pathogens. Nevertheless, the notion of a 'relevant target' largely depends on the interpretation of the observer. It was understood from the interviews there are four pivotal arguments necessary when building a case to select the target. These include; disease burden, knowledge availability, technological feasibility and the business case (Table 7.1). The 27 key opinion leaders (KOLs) completed a weighted-ranking exercise, in order to quantitatively indicate their point of view (Chapter 6).

Table 7.1   **Definition of motivators**

Motivator	Definition
Disease Burden	In the case of vaccines for infectious diseases, such as pandemic influenza, the size of the market is unpredictable. Any argument relating to epidemiology or demographics of the market as a motivator to start a novel R&D programme.
Knowledge Availability	Preliminary knowledge based on experiments and existing knowledge on the workings of the immune system. Any argument relating to the (limits of) existing knowledge as a motivator to initiate a novel R&D programme.
Technological Feasibility	This refers to the state-of-the-art and niche market position of the (novel) technology. Any argument relating to the (limits of) existing state-of-the-art as a motivator to initiate a novel R&D programme.
Business Case	Any argument relating to the business, strategy, investment opportunities or financial structures and frameworks that allow for the development of the drug, as a motivator to initiate a novel R&D programme.

Similarities and differences between the opinions of the KOLs are highlighted in the matrix (Figure 7.2; Chapter 6). Both the knowledge institutes and R-PHA representatives consider the bur-den of disease the most persuasive argument. The societal benefit is believed to be the only justification for these KOLs to initiate a vaccine project. Industry representatives are (by default) more concerned with the business case when deciding on the relevance of a target pathogen. Although disease burden is in second place, the survival of the company drives the perception on the relevance of the target (i.e. incremental innovations secure steady markets from repeat business). With this knowledge, start-up companies can select more specifically which stakeholder to approach for collaboration but will have to compete with in-house-developed lead and target compounds.

Figure 7.2   Matrix showing perceptions of KOL on project motivators.

The perspective of the knowledge institutes is taken as a reference. X-axis indicates motivators, listed in the ranking order of the knowledge institutes. Y-axis indicates ranking order of perceived importance; 1 indicates most important, and 4 least. Methods and justifications are described in: Chapter 6.
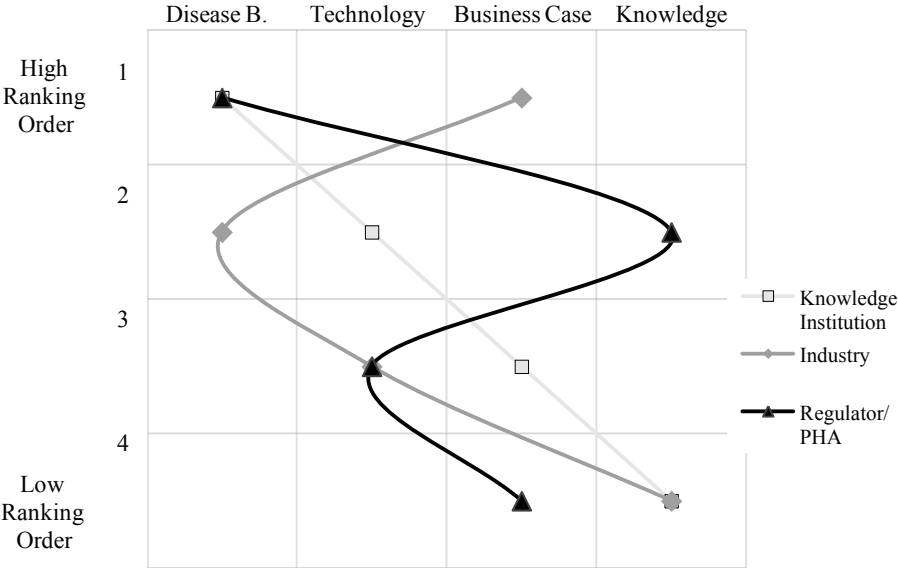
7.3.4 *Learn from Failure and Enjoy Success*

Last, but definitely not least: learning from failure. Sometimes, failing to overcome an obstacle is even necessary in order to proceed. Indeed, one successful vaccine is the sum of all previous discontinued projects. Moreover, none of the experts can recall a single vaccine project that was completed flawlessly. KOLs explain that it takes experience to identify rate-limiting factors, and to intervene when necessary. By definition start-ups have never failed before and therefore always need a truly vaccine experienced scientific and management team. Nevertheless, one should also be able to recognize a healthy project, and enjoy its success.

7.4   Conclusion

As re-emerging and emerging infectious diseases persistently threaten public health, relentless dedication by all players in vaccine R&D is necessary. In order to continue to address unmet medical needs it is pivotal to change vaccine development attrition rates. However, improving the odds is challenging in the fragmented and multidimensional value chain. Moderating the risks for project discontinuation all boils down to recognizing the rate-limiting factors and taking appropriate action. Insights into potential obstacles are greatly improved by planning ahead, keeping R&D simple, and valuating the appropriate target pathogen, thereby steering away from radical innovations. Moreover, KOLS firmly believe start-up companies should not have to re-invent the wheel. As such, very early collaboration with experienced stake-holders can drastically improve success rates.

Chapter Eight: Summarizing Discussion

8.1 Innovation Paradox in Vaccine Target Selection

When compared to NCE development, vaccine development is considered the most lucrative investment option within the scope of the biopharmaceutical industry [61]. In terms of the amount of resources invested, subsequent return rates, compound annual growth rates, length of development timelines and risk: vaccines unequivocally outshine the performance of NCEs on all dimensions [60, 61].

In essence, any activity aimed at developing a novel vaccine will generate a win-win situation for all involved. Prophylactic vaccines are unique in comparison to other therapies, in the view that the final product is acquired by national health authorities and the consumer segment consists of healthy individuals. From the perspective of the entrepreneur, manufacturer and investor; vaccines provide more value for every invested dollar when compared to that same dollar invested in an NCE [60, 61]. From the standpoint of the health care institutes and regulatory agencies; disease prophylaxis is more cost-effective than therapeutic symptom alleviation. Furthermore, appropriately directed vaccination campaigns are capable of eradicating an infectious pathogen from the face of the earth. An achievement valued highly by global society [49, 245].

Additionally, the potential applications for vaccination are expanding. First generation prophylactic vaccine preparations generally targeted paediatric and adult infectious diseases. Nowadays, newer generation vaccines are being developed for immunotherapeutic applications [22]. In light of the predicted biopharmaceutical industry trend towards personalized medicine, vaccine developers will inevitably be able to accommodate for this in the future.

When focusing on prophylactic vaccines targeting human infectious diseases, novel vaccine development is subject to the process of valorization. Valorization is the act of creating added value to the vaccine candidate as it successfully progresses from one development phase to the next (Glossary 1.3.6)[74]. Generally, valorization in the health- and life-sciences sector starts with a specific unmet need, want or demand. Unmet entities appear in the following areas; target infectious pathogen, manufacturing technology, antigen delivery technology and immunostimulating excipients/active compounds for example (Figure 8.1) [80]. As indicated in Chapter 2, it is dependent on the entrepreneurial style in which format the unmet medical entity will be addressed. The solutions are often sought after through realizing knowledge and/or technological inventions. In the case the solution consists of a vaccine candidate, it will have to complete the various stages of the value chain successfully before either the radical or incremental innovation may be awarded market entry. It is during the marketing-life cycle of the vaccine where its value and success are determined by the laws of supply and demand. Ultimately, vaccine accessibility determines whether the unmet entity has been adequately satisfied, at which point the valorization cycle repeats itself for another unmet medical entity [246].

Nevertheless, over the past two decades the biopharmaceutical industry has been affected by a so-called innovation paradox. It delineates the situation whereby the amount of inventions do not reflect the predicted output, as measured by the quantity of successful market entries [74]. This phenomenon has already manifested itself in the form of a

productivity gap, confirming that the increasing average investment in vaccine R&D activities far surpasses the anticipated product launches [99, 247]. One can only start to imagine the consequences of such imbalance. For example; opting for risk-aversive strategies and selecting only incremental innovations for further development [244].

Here we explore this innovation paradox, specifically focusing on vaccine target selection. The first section presents a brief theoretical overview on how needs, wants and demands are determined. The second section relates to how the unmet needs, wants and demands are addressed. The final sections describe the lessons learned and proposed future research topics.

Figure 8.1   Valorization Cycle
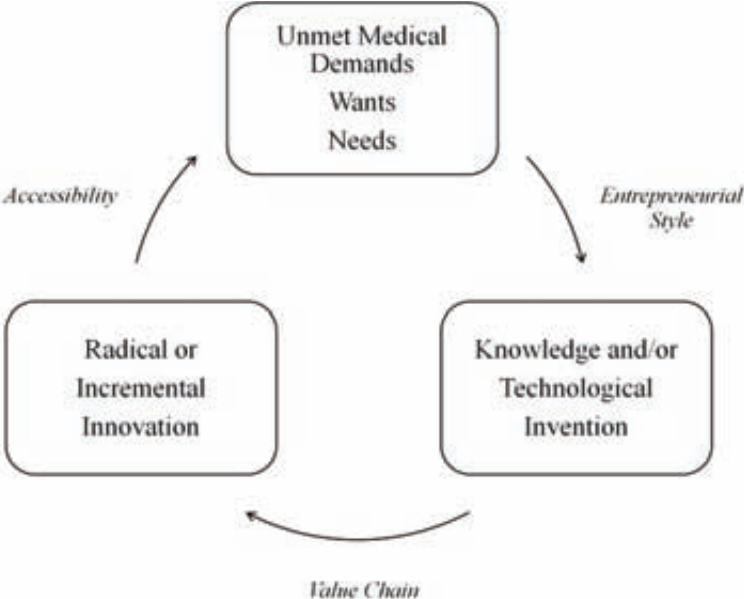
8.1.1 Determining the Unmet Medical Entity

Fundamentally; recognizing and identifying the unmet medical needs, wants or demands within the public health arena is influenced by the ruling scientific paradigm. A scientific paradigm is a theoretical frame-of-reference, universally acknowledged by the members of the scientific community, colouring all thoughts and practices within that period. It was a term first coined by historian Thomas Kuhn in 1962 [248], who observed that the evolution of knowledge and inventions occurs in cyclical episodes. As described in *The Structure of Scientific Revolutions*, a cycle involves periods of so-called normal science and revolution[248]. It is the latter which results in a paradigm shift; a period capable of altering the common discourse within the subsequent era of normal science.

A scientific paradigm is reflected in the technological and intellectual innovations within that particular normal or revolutionary cycle. Although discrepancies remain on specifically delineating scientific paradigm boundaries, the current state of the art - since the 1980s - is said to belong to the information-age [249-252]. In other words, technological and intellectual evolution is influenced by the discourse of that particular scientific paradigm. Furthermore, technological and intellectual innovations transition according to theories of industry and product life-cycles [253]. These are characterized by periods of expansion, stagnation and recession, where expansion is believed to be triggered by radical innovations or significant historical events [253, 254]. Even though only one scientific paradigm dominates, both industry and product life-cycles influence public life [255].

Given the present economic climate, it is believed we are currently experiencing a shift into a new cycle where efficiency and sustainability are considered the leading emotion [256]. Such a scientific paradigm shift already has repercussions on industry activities and related strategic decisions. For example, the biopharmaceutical industry is adopting strategies for prolonging company survival. Topics at the organizational-level of vaccine project development - such as the predictability of research and development (R&D) productivity and successful portfolio management outcomes - have become popular subjects of debate. Moreover, there is a shift from focusing on increasing the output of the vaccine value chain, to a combination of; maximizing the benefit of the output, reducing the input and increasing efficiency of the system. Additionally; the earlier along the value chain the decision on project discontinuation takes place, the more beneficial to society as a whole[257].

Where does this leave vaccine target selection? As published by Buchanan *et al* (2011); "depending on what is created, innovation (or lack of) can worsen existing injustices or create new injustices, or it can lessen existing injustices [30]." In view of the strong correlation between health and wealth [3], certain infectious pathogens are known as poverty-inducers, thereby highlighting the necessity for selecting appropriate target pathogen for vaccine development. In short, while the interpretation of the (re-) emerging and neglected diseases is dependent on the current scientific paradigm, the technological and intellectual state-of-the-art influences whether the unmet entity can and/or will be addressed.

8.1.2 Addressing the Unmet Medical Entity

The desired outcome of valorization is realizing a public health unmet need, want or demand. Whether innovation materializes as an action or a reaction to the unmet entity is beyond the scope of this dissertation. Nevertheless, we ask ourselves if valorization is capable of commercializing an appropriate innovative response to address the unmet medical entity.

When it comes to addressing the unmet entity, there is a distinction between the level at which the unmet medical entity is manifested, and the level at which valorization takes place. The relationship between the micro-level responses to macro-level issues is best understood using a philosophical causal-mechanism based explanation. A mechanism is generally defined in terms of both the effect produced, as well as the entities of a causal process that result in the effect of interest [258]. It is best visualized using Coleman's bathtub framework (Figure 8.2)[259].

Coleman's model illustrates the underlying analysis required for finding the causal mechanisms that lead to the desired macro-level phenomenon. It is believed that simply associating macro-phenomena with each other is insufficient (Arrow 1). Therefore an analysis of the so-called black-box is essential in order to understand the collective dynamics and interpret the micro-level and macro-level action-reaction reciprocity.

Figure 8.2   Coleman's bathtub and placement of chapters, adapted from [258]

Actor* indicates established organizations, start-up firms and entrepreneurs.
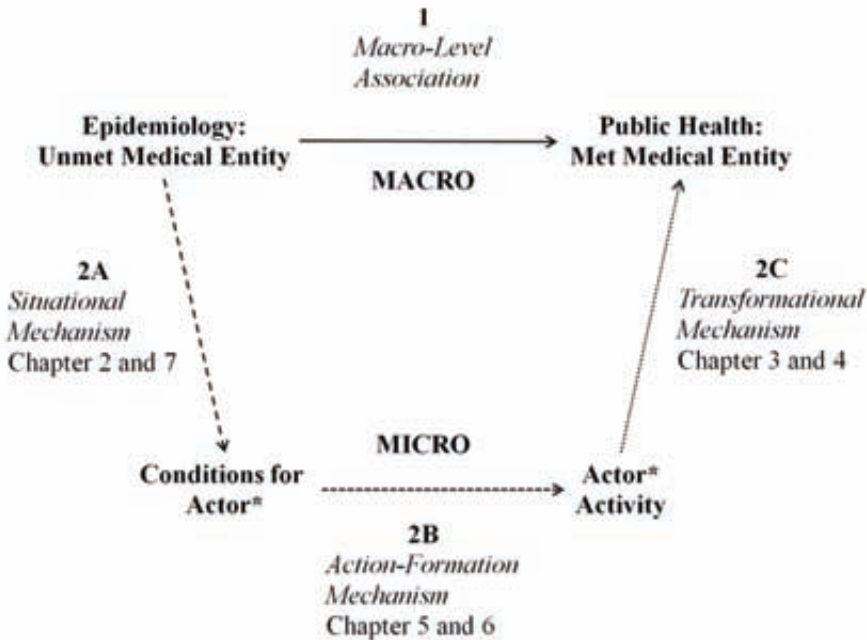
Actions at the micro-level generate both intended and unintended social outcomes at the macro-level [258]. This notion relates back to the philosophical principal of action. According to mechanism-based theories, an individual's action is primarily oriented as a reaction. Similarly, at the organizational-level, a firm's strategy is determined by the industry landscape within which it operates. However, actions are channelled by the structures surrounding the actor, influencing both motives driving the activity as well as shaping the anticipated outcome. Hence, the full impact of an actor's intended outcome can only be assessed by studying those structural elements. This consists of holistically evaluating the stages including the situational (Arrow 2A), action-formation (Arrow 2B), and transformational (Arrow 2C) mechanisms [258].

Given the interconnectedness of modern society, realizing prophylactic vaccines targeting infectious diseases generally affects the global community at the macro level. One unique feature of infectious diseases is their ability for transmission between humans. Taking *ceteris paribus*, healthy individuals have an equal chance of coming into contact with the natural pathogen and developing the infection. Although the reservoir for many infectious pathogens is unknown, the most efficient carrier is the (asymptomatic) infected individual. Human carriers allow for both epidemic and endemic infectious diseases to circulate within and between communities. As a result, realizing vaccine innovations reduces infection transmission, thereby inherently affecting the global population.

In the majority of cases, the answer to the public health unmet medical entity is provided by the private-sector. The response to the unmet medical entity is generally formed by vaccine industry and by entrepreneurs in start-up companies. With these actors representing micro-level activity, the individual research chapters in this dissertation cover specific segments of the black-box.

8.1.2.1 *Situational Mechanism*

Both *Chapter 2* and *7* describe the situational mechanisms shaping entrepreneur and firm action. To start off with, the theory-extending *Chapter 2* delineates the entrepreneurial contributions towards science-based venturing in vaccine R&D. According to Bracker *et al* (1982), three entrepreneurial typologies can be distinguished based on motivation and management styles [260]. These include the situational entrepreneur, the craftsman and the opportunistic entrepreneur [260]. By applying this framework to the context of valorization, it is evident the three styles inherently possess specific competences that are - logically - most effective at different stages of the value chain. Generally the entrepreneur should be able to recognize the opportune moments to enter, and exit, the vaccine value chain. It is during this window of opportunity the entrepreneur can contribute most effectively; on the one hand benefitting from relative low-entry costs, while on the other potentially maximizing returns.

Typically, during the initial start-up phases of a given vaccine candidate, the target disease selection is unrestricted. In fact, a former public health key opinion leader rationalized that at any point in time, research is ongoing on all of the known pathogens. Unfortunately, one of the situational mechanisms is attributed to the perception of risk. Translating fundamental research into a viable product - more often than not - leads to project

discontinuation. This is partially due to the unclear commercial potential of the novel vaccine candidate during these earliest stages of development. Particularly right after completing the pre-clinical development phase and before the vaccine candidate moves to the first-in-human clinical trials, it is challenging to attract investors and maintain a positive cash-flow. This infamous bottleneck can best be described as a tipping-point, most often colloquially referred to as the 'valley of death'[261].

Bridging the valley necessitates the adoption of the most effective risk- and project-management strategies for the evaluation of project viability. *Chapter 7* complements *Chapter 2* by offering insights into several strategies that could increase the likelihood of building successful ventures. Essentially this research chapter is aimed at entrepreneurs and start-up firms. It ameliorates four recipes to be taken into consideration prior to initiating a vaccine R&D project, including; planning ahead, keeping it simple, valuating relevance and learning from failure. Such recommendations will hopefully be extended into business practices, finding leverage within the current scientific paradigm.

8.1.2.2 *Action-Formation Mechanism*

The vaccine value-chain defines the action-formation mechanism. It describes the necessary chronological phases required to develop a product innovation up to the point of market entry. Both *Chapters 5* and *6* identify conditions that could influence the general productivity of the value chain. *Chapter 5* accounts for the timelines in clinical data management whereas *Chapter 6* provides an overview of the potentially rate-limiting factors encountered throughout the value chain. Although the challenges do not relate directly to vaccine target selection, in essence; any reason for project delay or discontinuation does affect the end-goal of attaining public health unmet entities. Nevertheless, it is clear that action-formation mechanisms are an under-developed area and could benefit from further research.

In the face of the first-time-right principal and associated development time pressure, *Chapter 5* contributes by researching data management efficiency in human clinical trial procedures. Although this is not a direct measure for organizational dynamics, data management systems are essential for compiling a dossier and have the potential to significantly impact value chain timelines. Focusing on a Clinical Phase I as executed by an academic research organization, it is believed the results are directly applicable in other clinical trial settings. Currently, 100% of the data points are subjected to intense examination by at least four independent institutions [262]. It is believed that selecting critical data points in advance will significantly reduce the amount of time spent validating and cross-referencing them during later stages of development. This chapter proposes a novel framework supporting an evidence-based approach; a number-needed-to-treat resiliency model for selecting critical data points that are directly related to the clinical endpoints. By pre-selecting data points eligible for sponsor queries prior to the start of the clinical study, the effect could lead to exponential time-conservation throughout clinical-experiment phase of the value chain. When taking into account all clinical trials around the world, implementing such a strategy could translate into potentially saving billions in financial resources.

Chapter 6 endeavours to uncover additional rate-limiting factors affecting adjuvanted-vaccine R&D. Although this topic is covered in the literature, a method with which to compare the rate-limiting factors with each other is lacking. Opting for a qualitative approach, 27 key opinion leaders were approached representing the knowledge institutes, industry and regulatory/public health authorities (R/PHA). Each expert within the field of adjuvanted-vaccines was interviewed on how they perceive the magnitude of the rate-limiting capacity of the factors. In essence, the interviews were designed to capture the self-interest component as supported by the principal-agent theory (PAT). The opinions were quantified using an effective weighted-ranking technique in order to indicate the top-ten rate-limiting factors. Subsequently the perceptions on the rate-limiting factors are plotted in a matrix-configuration, to visualize the differences in opinion. Analysis into the interview transcripts reveals four reasons underlying this difference, namely; risk management, innovation strategy, valuation and funding.

One of the more significant observations from *Chapter 6* is the supply-driven value chain configuration. Based on PAT, the relationship between the three expert groups is diagnosed with a partial agency-problem. Partial in the sense that there are conflicting interests between the internal preferences of each of the three groups, yet novel adjuvanted-vaccines have recently been awarded market authorization. Nevertheless, the agency-problem leads to more stringent risk management strategies. This is reflected by the choice in the target disease areas currently in the development pipeline, which favours me-too markets [224].

Solutions to agency problems are generally the following: monitoring to evaluate information symmetry, alignment of interests and bureaucracy [198,199]. A proposed solution to the conflicting interests is found by converting the value-chain into a demand-driven configuration, thereby essentially aligning interests (Figure 8.3). Ideally in the demand-driven state the unmet medical entity (e.g. epidemiological data) is added to the system and will be regarded as the principal. Consequently, the information asymmetry existing between the knowledge institutes, industry and R/PHA will also be reduced. The three agents would interact in order to satisfy the common goal as set by the principal. In this case, it would be meeting an unmet medical entity. This, however, should not interfere with the original purpose of each of the agents; the knowledge institutes would carry on conducting fundamental research, the industry would remain profit-seeking entities, and the R/PHA would continue to regulate and monitor the safety, efficacy, quality and ethical parameters of value chain procedures. Ultimately, such an approach could result in broadening the portfolio of targets selected for vaccine development.

Figure 8.3 Demand-driven value chain configuration

The unmet medical entity is considered the principal, and the knowledge institutes, Regulatory/Public Health Authorities and Industry are considered the agents.
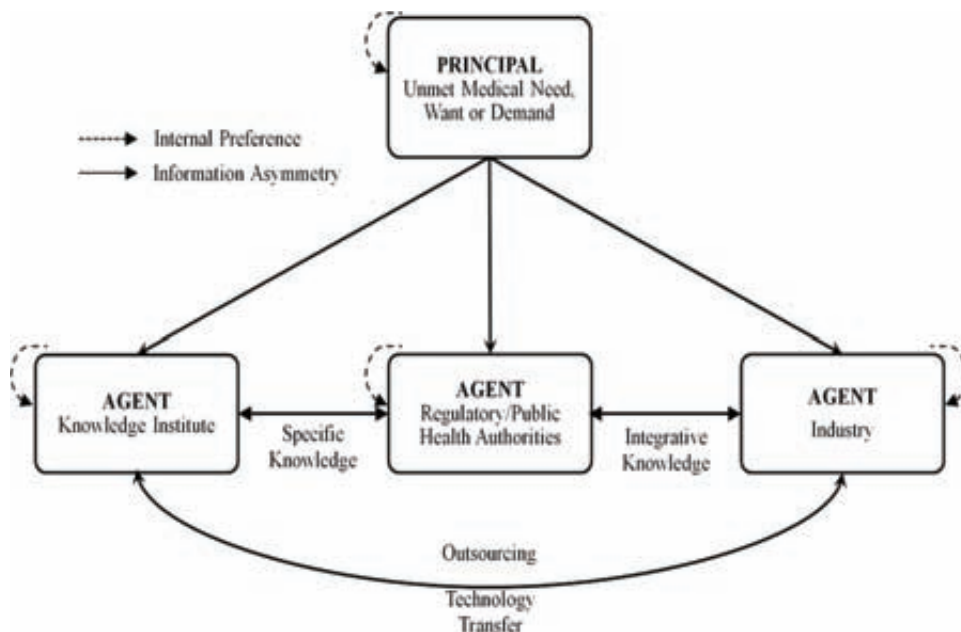
8.1.2.3 *Transformational Mechanism*

In this dissertation, both *Chapters 3* and *4* provide tools for calculating the productivity of organizational activity. Data on successful market entry is used as a measure of productivity, which in turn is used to indicate the efficiency of the transformational mechanism. Nevertheless, being awarded market authorization is only the first step. In order to fully comprehend the transformational mechanism, the impact of vaccine accessibility in local communities should also be taken into account. This latter aspect falls beyond the scope of the research in this dissertation, yet is covered by the access framework as published by Frost *et al* (2004) [263].

To start off with, *Chapter 3* reviews the literature on organizational productivity. Seven publications were identified, reporting market entry success rates reflecting the productivity of the new chemical entity (NCE) value chain. Productivity rates are taken as the ratio between the input and output of the value chain. The results range wildly from 7% to 78%. Further analysis reveals that the methodologies differ along the dimensions of data set in- and exclusion criteria as well as the consideration of the in- and dependent variables. Although the data are said to express the same measure of productivity, clearly a standardized calculating protocol is lacking. Nevertheless, such calculations ultimately confirm the existence of the productivity gap, even if a consensus is lacking regarding the severity of the paradox.

In the majority of publications it is unclear whether vaccines have been incorporated in the datasets. Only one article from 1996 explicitly focused on vaccine development success rates, calculating a probability of 22% [264]. *Chapter 4* can be seen as an extension of the previous chapter, by defining the organizational-level productivity to fit vaccine development specifically. For the purpose of this dissertation, productivity is defined by the cumulative rate of vaccine candidates successfully transition from the pre-clinical phase up to the point of market registration. Without the intension of forecasting a trend, our dataset implicates a success rate of 6%. This indicates a substantial productivity gap in the value chain, tailored exclusively for vaccine candidates.

If this crude statistic is to be compared to the NCE productivity rate as published by Dimasi (2003), perhaps investors might hesitate before investing in vaccine development[110]. Nevertheless, investors seeking strategic financial advice should take additional confounding variables into consideration, adding extra dimensions to the concept of productivity. For example, stratifying data into chronological value chain phases and disease areas. This allows for highlighting common developmental opportunities - as well as the bottlenecks - shared by vaccine candidates within specific disease areas. Additionally, the average vaccine requires only half the total investment that it would take a NCE to reach the status of market registration. This implies that the financial risk for investing in vaccine development is less when compared to that of NCEs[242].

8.1.3   *Final Thoughts and Implications*

The productivity gap is often viewed as an unfortunate symptom of an inefficient vaccine development system. Some research groups support the notion that the productivity gap is a consequence of the value chain itself. They argue that the classical, linear value chain can benefit from being restructured [265]. Solutions proposed include an iterative proof-of-concept phase [266, 267], question-based drug design [64] and prototypical drug development [268]. Other groups believe that the productivity gap is a consequence of the unknown, confounding factor. For example the target disease area; vaccine developers are believed to have exhausted the list of relatively easy disease targets - the so-called 'low-hanging-fruits'. Consequently, the remaining targets are considered relatively more complex, which translates into higher attrition rates [269, 270].

To our knowledge, we believe that the origin of the innovation paradox in vaccine target selection cannot be traced back to one single cause. The paradox can only be fully comprehended once the entire valorization cycle - of which the vaccine value chain represents one component - is taken into consideration. In other words, one would not work from a linear value chain but rather from an all-inclusive cycle. Such an overview allows for holistically examining the innovation paradox from a multidisciplinary perspective, making it possible to identify several causes that contribute to the productivity gap.

The valorization cycle delineates a number of sequential steps in the transfer of technology from the symbolic 'bench to bedside' and back again, while simultaneously accumulating

value (Figure 8.4). All ten steps are considered equally important, reinforcing each other as the vaccine candidate transitions from one to the next. If one of the steps were to be eliminated or skipped, it would naturally follow that the cycle disintegrates and the vaccine is arrested in that stage of development. Moreover, the cycle is sub-divided into three distinct segments, based on the discourse dominating that particular valorization aspect. These include the scientific, economic and market and policy discourse. Although each of the steps within a segment inherently possesses attributes that could lead to project discontinuation, the innovation paradox manifests itself at the interface between segments.

For the sake of illustrating the rationale, valorization starts at the idea stage (Step 1). In the case of high-tech vaccine development, this idea would most likely originate within the scientific discourse. The invention - whether it is technological or knowledge based - should motivate the individual to take empirical action (Step 2a and b). Nevertheless, the type of activity required to evaluate an idea is inevitably shaped by the situational mechanisms, and the individual's entrepreneurial style [242]. Once the invention has been favourably assessed in terms of its feasibility and viability, it will eventually materialize into a patent, publication, report or product (Step 3).

It is at the intersection between the realization (Step 3) and the proof-of-concept stages (Step 4) where the dominant discourse changes. Whereas the previous three steps focus on developing the scientific aspect, the discourse in the fourth step is oriented towards economic and commercial disciplines. It is at this point in the cycle that the inventor starts negotiating with another, more profit-seeking culture of investors and related stakeholders. This barrier should not be confused with the valley of death, which takes place after the pre-clinical development (Figure 8.4; between step 4 and 5). In the case of the first-time start-up firm, spin-off company or entrepreneur, having to learn this completely new dialogue represents a certain level of commitment. Similarly in an established firm, the invention would be translated by a scientific liaison officer to a more senior management level.

In both scenarios the value of the invention has to be translated from one discourse into the next. If the message is misunderstood by the receiver, the process loops back to the metaphorical drawing board. This loop is also referred to as the Dutch innovation paradox. In short; while research institutes in the Netherlands rank sixth place in the global innovation index of 2012 [271], somehow commercialization of the invention scores low-to-mediocre when compared to the performance of other countries [272]. Several key opinion leaders affirmed that at this interface there is no way of knowing the outcome of a decision. The one invention that is discontinued might have turned out to be life-saving, whereas the one that is selected to proceed still has a chance of getting discontinued along any of the subsequent steps (Step 4; proof-of-concept, Step 5; evaluation and Step 6; up scaling) [273]. Perhaps the difference in discourse partially accounts for the inefficiency in overcoming the Dutch innovation paradox.

The second segment - describing the action-formation mechanism - is dominated by economically oriented discourse. As elaborated by *Chapters 5* and *6*, this portion of the valorization cycle holds numerous rate-limiting elements. Essentially, this is when the vaccine candidate undergoes a series of rigorous experiments. Not only does this filter

remove the weaker candidates, it simultaneously reinforces and strengthens the value of the successful vaccine candidate. The crude measure on productivity - in terms of absolute market entries (*Chapter 3* and *4*) - merely establishes the efficiency of this economic segment.

Ultimately the success of a vaccine is influenced by its introgression into the market (Step 7). At this intersection it is believed the innovation paradox is less dependent on the communication barriers between the two segments. One of the reasons is that fact that economic activities are naturally directed towards market entry, and are therefore better informed on market and policy discourse. It is the accessibility that contributes to the innovation paradox. The framework as published by Frost *et al* (2004), and later elaborated on by Morel *et al* (2005), describes this bottleneck in terms of accessibility, availability, affordability and architecture [263, 274].

The third section of the valorization cycle essentially focuses on the transformational mechanism. Once the vaccine has been awarded market authorization, and is accessible to the target population, the dynamics of the market landscape changes (Steps 8 and 9). Such changes necessitate continuous evaluation of the market, and this information feeds into the perception of the (un-)met medical entity (Step 10).

Interpreting the unmet medical issue is influenced by the scientific paradigm in which the market and policy discourse exists and agenda setting as well. According to the agenda setting theory by McCombs *et al* (1972); the ranking of issues is dependent on the source of the information, which in turn influences the perception of reality [275]. Demand articulation is therefore influenced by the somewhat hidden agendas of the media, public, commercial and policy spheres.

Since we consider valorization as a cyclical process; any met issue ultimately reveals another unmet one. Schmidt *et al* (2007) rationalizes that there are an infinite number of unmet problems [276]. Unfortunately there are physically insufficient resources available to address all unmet issues, given the current vaccine value chain and development practices[276]. Such arguments emphasize the need for interpreting the unmet issue appropriately in order to allocate resources as efficiently as possible. Ultimately, from the pool of unmet entities, only a few will be articulated.

The final contributor to the innovation paradox materializes at between the demand articulation (Step 10) and idea generation (Step 1). This is where the valorization cycle comes full circle, and where the third and last discourse boundary has to be crossed. This communication barrier between the market and policy discourse and the scientific discourse is influenced by supply-driven principal-agent relationships (*Chapter 6*). The agents select the unmet medical issues based on their internal preferences, most commonly through incrementally building on previous innovations. In this current system, unmet problems ARE being addressed; however it is a question of whether this response truly corresponds to the unmet medical needs at the societal-level. One proposed solution is the demand-driven value chain configuration, which allows for the agents to act directly on the unmet issue from the epidemiological source.

Figure 8.4   Valorization Technology Transfer Cycle, adapted from Claassen (2008).

The grey areas indicate the dominant discourse within the respective valorization steps

*   Frost and Reich (2004) access framework [263]

**   McCombs (1972) theory on agenda setting [275]
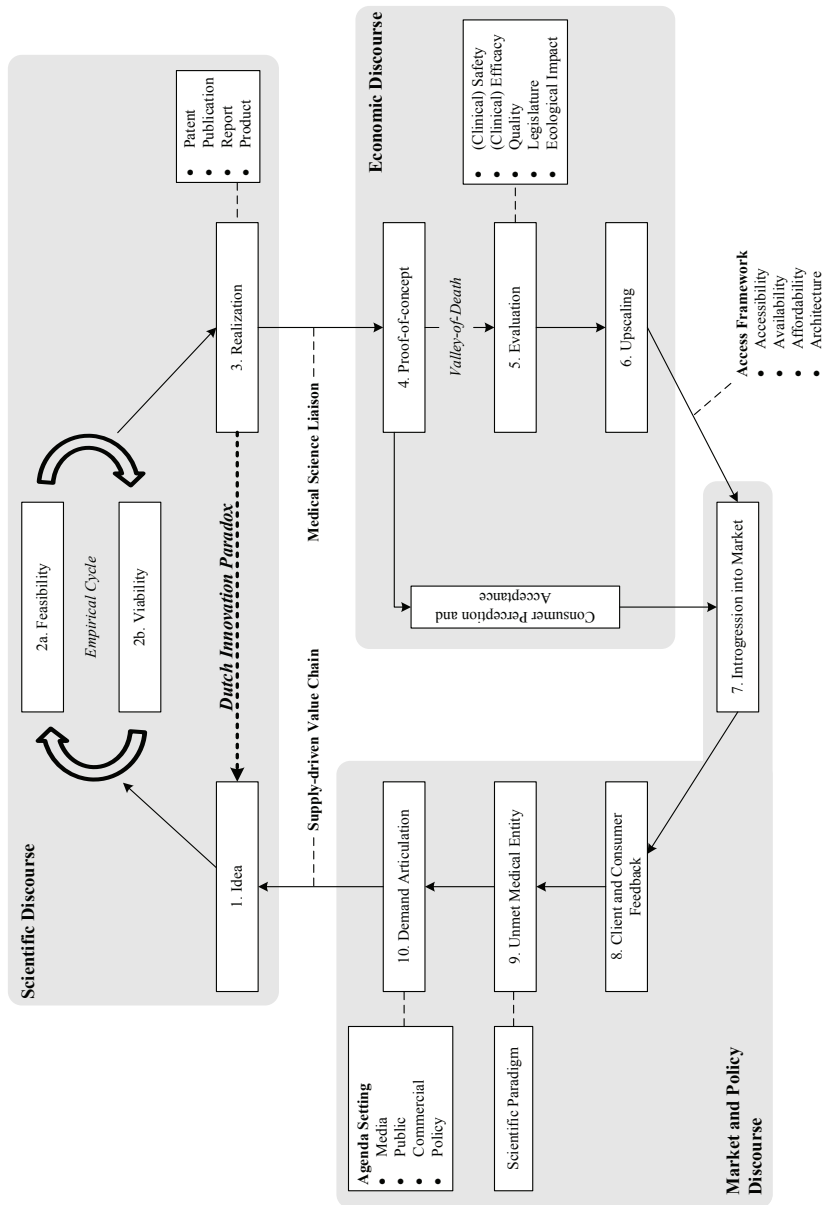
Lessons Learned

The Innovation Paradox in vaccine target selection is best viewed using a holistic, multi-disciplinary perspective. There is not one single cause that can be identified as the main instigator to the productivity gap. By taking the whole cycle into account there are numerous bottlenecks that affect productivity. These include the medical science liaison, access framework and supply-driven value chain.

Technology transfer is essential in the valorization process of innovations. Only through proper guidance will the inventor be able to overcome the economic discourse barrier and have a shot at commercializing the invention. Effective communication regarding both the specifics of the invention, and value is decisive at this interface.

Clinical data management can benefit from a number-needed-to-treat resiliency model to identify high-risk data points. Pre-selecting data points that are critical to the understanding of statistical outcome of the clinical trial is considered more efficient than the current 100% verification by several independent institutions. This would significantly save resources and reduce development timelines.

Weighted ranking is an effective tool for converting qualitative information into quantitative data. Moreover it supports the principal agent theory in terms of capturing the self-interest component of the principal and agents, while simultaneously visualizing the results using a matrix-model. Weighted-ranking is a widely used tool within the social sciences, yet this manuscript demonstrates its function within the economic and management research disciplines as well.

Risk profiles are useful tools when it comes to illustrating and evaluating the productivity of vaccine and NCE development. Productivity is defined as the output generated by the input. The risk profiles combine the transition probability of a vaccine or NCE candidate from one value chain phase to the next, with either; the investment required for that particular phase, or the duration a candidate remains in that particular development phase. Visualizing such data in a graphical form provides an overview of the value chain procedures and allows for identifying common bottlenecks. Moreover it allows for investigating the impact of numerous other variables and their effect on the risk profile.

Suggestions for Further Research

The innovation paradox in vaccine target selection could benefit from research covering the medical science liaison gap and evading the Dutch Knowledge Paradox trap. According to recent meta-analysis by Evanschitzky, *et al* (2012), new product success factors include; product, strategy, process, marketplace and organization [277, 278]. Especially during the fuzzy front-end stages; enhancing the effectiveness of valorization technology transfer activities can be seen as one of the main strategies that could contribute to reducing the productivity gap. One of the proposed research topics includes the difference in discourse between the realization and proof-of-concept steps, is communicating the potential value of the patent, publication, report and/or product.

A second proposed research topic would entail the transformational-mechanism, focusing specifically on the accessibility of vaccines and the diffusion of knowledge and technology in both high-income economies (HIE) and low-to-medium income economies (LMIE). Currently vaccine manufacturing landscape is an oligopoly, whereby vaccine development expertise is concentrated within five multinational biopharmaceutical companies from high-income economies (HIE). Intensified merger and acquisition activities [279], as well as substantial barriers for start-up firms entering this high-tech industry, are examples that contribute to a reduction in the number of players, thereby reinforcing the oligopoly. Consequently, a handful of companies influence the portfolio of disease targets available to first-time vaccine developers. In terms of vaccine accessibility; once the vaccine is manufactured - generally by HIE vaccine manufacturers - there is an average lag-period of 15 to 20 years between the initial market introduction of a vaccine in the private market (usually HIE) to the final general-use and public market access phase (usually LMIEs)[280,281]. When taking vaccines targeting *Haemophilus Influenzae Type B* as a case study; vaccine manufacturers in LMIEs are also capable of delivering a substantial quantity of dosages, thereby reducing the lag period substantially. Nevertheless, few studies analyze the vaccine market based on diffusion of innovation and technology theories. In the view of the changing vaccine manufacturing landscape, this presents a critical area for further analysis.

Samenvatting

De volksgezondheid wordt continu op de proef gesteld door nieuwe en terugkerende infectie ziekten. Een bijkomend groeiend probleem is de resistentie van pathogenen tegen de beschikbare behandelingen, waaronder vaccins. Deze aanhoudende en bedreigende onvervulde medische behoefte daagt vaccin ontwikkelaars uit om in te spelen op toekomstige epidemieën. Er zijn echter onvoldoende middelen beschikbaar om alle onbeantwoorde medische vraagstukken aan te pakken. Zo duurt de ontwikkeling van het gemiddelde vaccin van 'bench to bedside' ongeveer 10 jaar, en lopen de kosten op tot meer dan € 400 miljoen. Vaccinontwikkeling wordt bovendien beïnvloed door de zogenaamde innovatieparadox: het aantal innovaties groeit terwijl de te verwachten uitkomst - voldoende succesvolle gecommercialiseerde producten - achterwege blijft. Deze situatie is gedurende de afgelopen jaren steeds duidelijker naar voren gekomen en heeft een significante invloed op de productiviteit van vaccine valorisatie, die hierdoor achterblijft. Gezien het positieve verband tussen volksgezondheid en welvaart, is het van cruciaal belang om het juiste ziektegebied te selecteren voor vaccine ontwikkeling.

Dit proefschrift bespreekt deze innovatieparadox in het kader van de selectie van menselijke infectieziekten voor de ontwikkeling van vaccins. Als het gaat om selectiecriteria van de desbetreffende infectieziekte, kan er een onderscheidt gemaakt worden tussen het niveau waarop de besmettelijke ziekte zich manifesteert (maatschappelijk-niveau), en waar valorisatie plaatsvindt (ondernemerschaps-, en organisatorisch-niveau). De actie-reactie wisselwerking tussen deze macro- en micro-niveaus ligt in het hart van de innovatieparadox. De zes hoofdstukken onderzoeken vaccin valorisatie vanuit het standpunt van de ondernemer en de organisatie. De nadruk wordt gelegd op strategieën die potentieel het selectie proces stimuleren of beperken. Daarnaast stellen wij dat het valorisatie proces doelmatiger wordt als het een allesomvattende cyclus is. Zo worden er een aantal opeenvolgende stappen voorgesteld die het proces van bench-to-bedside en weer terug begeleiden. Hierdoor wordt de onvervulde medische behoefte nauwkeuriger gedefinieerd en kan er een accurate inschatting gemaakt worden van de benodigde middelen en de manier van aanpak. Evengoed is het aan de biofarmaceutische gemeenschap om in de opeenvolgende stappen zijn innovatiekracht te blijven tonen en daarmee veilige en effectieve vaccins te ontwikkelen ten behoeve van de volksgezondheid.

Summary

Public health is continually threatened by re-emerging and newly emerging infections, as well as pathogen resistance to available intervention strategies, including vaccines. This persistent threat of the unmet medical need challenges vaccine developers to anticipate future epidemiological outbreaks. Nevertheless, there are insufficient resources available to address all unmet medical needs: developing the average vaccine candidate from the symbolic 'bench to bedside' takes approximately 10 years requiring an investment exceeding €400 million. Furthermore, vaccine development is affected by the so-called innovation paradox. In short; regardless of increasing research and development activities, the predicted output - as measured by successful market entry of the commercialized product - is lacking behind. This situation has intensified over the past few decades and significantly impacts the productivity gap in vaccine valorization. In the view that there is a correlation between health and wealth; it is critical to select the appropriate target disease area for vaccine development.

This dissertation evaluates the innovation paradox in selecting human infectious disease targets for vaccine development. When it comes to selecting the target, there is a distinction between the level at which the infectious disease is manifested (societal-level), and the level at which valorization takes place (entrepreneurial- and organizational-level). This action-reaction reciprocity between the micro- and macro-level lies at the heart of the innovation paradox. The six research chapters offer an assessment into entrepreneurial- and organizational-level productivity, focusing on strategies that would potentially stimulate and restrict vaccine target selection. Additionally, we propose the valorization process would be more efficient as an all-inclusive cycle, delineating a number of sequential steps from bench-to-bedside and back again. Such a cycle would allow for proper assessment into the available resources, in order to most accurately determine and address the unmet medical need. Nevertheless, it is up to the biopharmaceutical community to demonstrate their innovative capacity within the context of valorization in order to continue to develop safe and effective vaccines for the benefit of public health.

About the Author

Esther Sophia Pronker was born on the 6th of October 1985 in Nieuwegein, The Netherlands. She completed primary education in Francophonic Abidjan, Ivory Coast and secondary education in Anglophonic international schools in Jeddah, Saudi Arabia. At the turn of the millennium she returned to The Netherlands where she completed an International Baccalaureate Diploma with high distinction, and continued to pursue a double Bachelor of Science degree in Biochemistry and Immunology at the University of Utrecht in 2007, graduating with high honours. After receiving her Master of Science degree in Management, Policy Analysis and Entrepreneurship in Health and Life Sciences at the Vrije Universiteit Amsterdam in 2009, Pronker started a PhD programme. Under the supervision of Prof. dr. Eric Claassen, Prof. dr. Harry Commandeur, she conducted research on the topic of the innovation paradox in vaccine target selection. During the programme Pronker had the opportunity to present her work at the 2011 ESWI conference in Malta, and the 2012 MVADS conference in Copenhagen. Moreover, she was invited as a guest lecturer at the Vrije Universiteit Amsterdam and the University of Toronto, Canada. From June 2013, Pronker will work at Viroclinics Biosciences BV as director business developer.

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INNOVATION PARADOX IN VACCINE TARGET SELECTION

Public health is continually threatened by re-emerging and newly emerging infections, as well as pathogen resistance to available intervention strategies. This persistent threat challenges vaccine developers to anticipate future epidemiological outbreaks. Nevertheless, there are insufficient resources available to address all unmet medical needs. Furthermore, vaccine development is affected by the so-called innovation paradox, significantly affecting vaccine valorization productivity. In the view that there is a correlation between health and wealth; it is critical to select the appropriate target disease area for vaccine development.

This dissertation evaluates the innovation paradox in vaccine target selection. When it comes to selecting the target; infectious diseases are manifested at the macro-level, for which valorization solutions are pursued at the micro-levels. This micro- and macro-level action-reaction dynamic lies at the heart of the innovation paradox. The six research chapters offer an assessment into entrepreneurial and organizational micro-level productivity, focusing on strategies that stimulate or restrict vaccine target selection. Additionally, we propose the valorization process would be more efficient as an all-inclusive cycle, delineating a number of sequential steps from bench-to-bedside and back again. Such a cycle would allow for proper assessment into the available resources, in order to most accurately determine and address the unmet medical need.

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