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DEPARTMENT OF FOOD AND RESOURCE ECONOMICS
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IFRO Report

Economic analysis of developing a Campylobacter vaccine to poultry: a real options approach

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Contents

Preface 4
Summary and conclusions 5
1. Introduction 11
1.1. Background 11
1.2. Economic benefits of a Campylobacter risk reduction 13
1.2.2. Valuation of non-market benefits 15
1.2.3. Economic benefits from international trade effects 17
1.3. The development of a new Campylobacter vaccine 18
1.3.1. The cost structure of a new vaccine 19
1.3.2. The pricing of vaccines 20
1.4. Organisation of the report 21
2. Systems analysis of the development and launch of a new Campylobacter vaccine 22
2.1. Main stages in the development process 22
2.2. A decision tree representation 24
2.2.1. Decision tree for R&D 26
2.2.2. Decision tree for patent application 27
2.2.3. Decision tree for testing 28
2.2.4. Decision tree for documentation and approval 29
2.2.5. Decision tree for production and distribution 30
3. Expected costs of a Campylobacter vaccine 32
3.1 Costs associated with the development 32
3.1.1. Research and Development (R&D) costs 32
3.1.2. Patent costs 34
3.1.3. Testing and documentation costs 36
3.1.4. Production and marketing costs 40
3.2. Market potentials for a broiler vaccine 42
3.2.1. Prevalence of Campylobacter 42
3.2.2. Economic margins in European broiler production 45

3.2.3. Demand curve patterns for the developed vaccine 46
3.3. Expected net present value of the developed vaccine 48
4. Real Option Valuation 51
4.1. Introduction 51
4.2. Shortcomings of traditional economic valuation methods 52
4.2.1. Investment decisions in biotechnology firms 53
4.2.2. Limitations of decision tree models for investment evaluation 54
4.2.3. The estimation of capital costs in discounting 55
4.3. Real options in the development of new vaccines 56
4.3.1. Characteristics of real options 56
4.3.2. Classification of real options 58
4.3.3. Real compound options embedded in vaccine development 60
4.4. Valuation of real options 63
4.4.1. The Black-Scholes formula 63
4.4.2. Binomial option valuation 65
4.4.3. Valuation of the compound option 71
4.4.4. Valuation of additional options 74
5. Discussion 77
5.1 Critical factors in the costs of veterinary vaccine development 77
5.2. Implications for business 79
5.3 Policy implications 80
References 82

Preface

Campylobacter *jejuni* stemming from poultry meat is an important cause of food-borne infections, leading to diarrhoea, stomach pain and cramping. Several types of interventions have been suggested to reduce the occurrence of Campylobacter in broiler production. The research project, *Campylobacter vaccination of poultry (CamVac)*, coordinated by professor Jeffrey Hoorfar from the Technical University of Denmark, has been carried out with the purpose of developing a vaccine to be applied to the birds in order to reduce the prevalence and concentration of Campylobacter in the poultry meat. The project has obtained funding from the Danish Council for Strategic Research.

As part of the CamVac project, the Department of Food and Resource Economics has been responsible for undertaking economic analyses related to the development of such vaccine, and this report presents some of the results from these economic analyses. The report has been prepared by associate professor Jørgen Dejgård Jensen, associate professor Mogens Lund and PhD fellow Ole Fabricius.

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April 2014

Henrik Zobbe

Summary and conclusions

Total and per capita consumption of chicken meat has grown strongly during the last several decades as a result of changing food preferences, increasing household income and population growth, and poultry is expected to become the largest meat sector worldwide in the decade towards 2021. Campylobacter *jejuni* stemming from poultry meat is an important cause of food-borne infections, leading to diarrhoea, stomach pain and cramping. Several types of interventions have been suggested to reduce the occurrence of Campylobacter in broiler production. Vaccination of the chicken is one such type of intervention, which is relatively new, and which thus had modest exposure in the literature. The objective of the report is to investigate the costs of developing, producing and marketing a Campylobacter vaccine to be applied in broiler production, taking into account the range of uncertainties involved in these stages.

Until now EU has adopted an integrated approach regarding food safety from farm to fork with the overall goal to protect the consumers from the food-borne zoonoses. This integrated approach consists both of risk assessment and management measures involving all key actors. Furthermore, this approach is complemented with timely and effective risk communication activities (EFSA, 2010). There exist already numerous intervention methods for reducing the Campylobacter in broiler chickens and broiler meat both on farm level and during the slaughter process. However, the epidemiological characteristics of Campylobacter and the cost-effectiveness of existing intervention methods provide the reasons to postulate that an effective vaccination strategy for infected poultry flocks may be the most effective means of preventing the human diseases from Campylobacter. Experimental vaccines mainly based on killed whole cell cultures have been tested in poultry but provide only partial protection against Campylobacter. Therefore, the development of a weakened live strain may be more promising although not yet commercially available (Els et al., 2007).

Vaccination can be seen as a way to avoid the high costs of a disease and also to enhance food safety to the society. The aim of such vaccination should be to protect the chickens from exposure from an early age, to eliminate colonization by the time of slaughter and/or to reduce the concentration of bacteria in the meat. A huge number of challenges are associated with the development of a new Campylobacter vaccine for broiler production. The market for veterinary vaccines is limited in size and spread across different types, and the development of vaccines becomes more and more complex and expensive over time (O'Brien & Zanker, 2007).

Vaccines are biological agents. Storage is costly and time limited, and adjustment of productive capacity is slow, costly and governed by regulation. Production is characterized by economies of scale and is subject to large-scale errors (batch failures). Because new vaccine development is a lengthy process, only a small fraction of all vaccine candidates are marketed in the end. Reasons for research abandonment may be grouped into different categories, such as safety e.g. human or animal toxicity;

efficacy e.g. activity of vaccine too weak or lack of efficacy; and economics e.g. the commercial market too limited or yielding insufficient return on investment.

Estimating the costs of developing, testing, producing and launching a new vaccine involves several challenges. A way to estimate the cost of developing a vaccine is to use benchmark data from the industry. The development of a new product may take from eight to ten years (O'Brien & Zanker, 2007). Overall, the new product during the development period has to demonstrate safety, quality and effectiveness, so it finally can be approved by the authorities before the launching. Because of the competition, the veterinary pharmaceutical industry is however not very likely to share information about their specific development costs (Madsen, 2012). Over time the adopted technology improves and therefore the regulatory requirements also become complex, leading to even higher cost of developing a new vaccine, but on the other hand, new technologies can possibly speed up the process and save time and costs in the longer run.

Systems analysis of the development and launch of a new vaccine

Biotechnology firms are facing major market and private risks in the development and launch of new vaccines and drugs in general. Market risks relate to e.g. the size and scope of the market, regulatory issues, consumer expectations and pricing, intellectual property rights (IPR), as well as competition through generic and copy products. Private risks include technological risks such as technical feasibility and failure risks as well as financial, organisational and managerial risks. A systems approach has been adopted to identify and evaluate the effects of this complexity of risks and their associated relationships on the costs and benefits related to the development and launch of a new Campylobacter vaccine.

From a systems perspective the development and launch of a new Campylobacter vaccine can be decomposed into a number of sequential subsystems. Overall, it is assumed that the development and launch of a new Campylobacter vaccine consists of basically six distinctive phases: (1) Research and development; (2) Patenting; (3) Testing activities; (4) Documentation and approval; (5) Production and distribution of the vaccine; and (6) further updating and testing activities to maintain the efficacy and safety of the vaccine (which has not been included in our systems analysis). At each stage during the development there is a possibility of failure due to a large number of risks. In the R&D phase, for example, there is the risk that no efficient organism is found to target the disease or that the formulation of the vaccine is unstable. In the patent phase there is a risk that the patent application is rejected as similar patents already exist or have been submitted for approval. All such risks imply that the course of the development process is not completely predictable at the outset, implying that decisions and strategies have to be made to cope with these risks.

Expected costs and benefits of a Campylobacter vaccine

The overall R&D expenditure budget for the whole project is crudely estimated to be 1.9 million € for biological and experimental R&D activities, of which salaries constitute about half, operating expenses one quarter, and administrative costs another quarter.

A broad estimate of the cost of a patent application is about 67.000 € including different application fees and refunds. Further comes more costs like printing fees and other fees to maintain the patent in the entire patent's lifetime of 20 years, and hence that the total patenting costs amount to 137,000 €. The total time frame of the entire patent phase is assumed to be at least four to five years on a vaccine patent case without major problems during the different steps. By nature, the patenting costs can vary considerably according to the decided type of patent and whether protection is national or covers the entire European Union.

In order to obtain marketing authorization for a veterinary medicinal product, the applicant should be able to document the properties of the vaccine. In the European Union, the documentation requirements are in principle similar to those for human vaccines with respect to safety attributes. The testing procedure can be separated into three phases: 1) Laboratory testing, 2) sub-clinical testing under controlled conditions, and 3) clinical testing under real production conditions. The costs of the first testing phase are estimated to about 152,000 € (including costs of developing a testing protocol and production of a vaccine for the testing process). Costs of the sub-clinical trial phase are estimated to be 31,000 € and costs of clinical testing amount to 58,000 €. On top of the testing costs come costs of preparing the documentation, which is estimated to be about 50,000 € that should be added to the testing costs**.**

The costs of production – and marketing – of a new vaccine depend on the life cycle of the product, capacity utilization in production, as well as several other factors. The price of existing live vaccines for poultry on the Danish market is 0.01-0.02 €/dose. Market experts estimate that marketing and distribution costs amount to about one third of the market price of such a vaccine, and that such marketing efforts are necessary to obtain sufficient sales. If we assume that full-scale production of the Campylobacter vaccine can be done at a cost similar to that of existing live vaccines, this implies a production cost of 0.8 eurocent/dose, and a distribution/marketing cost of 0.5 eurocent per dose.

The market potential for a Campylobacter vaccine in broiler production is assumed to depend on the total broiler production, the current prevalence of Campylobacter in broiler flocks, and the potential economic gains of primary producers of delivering Campylobacter-free broilers to the processing stage. We distinguish three different scenarios, reflecting three alternative marketing strategies in terms of geographical orientation. The first scenario covers all EU-27 member states, the second scenario assumes that the vaccine is primarily aiming at Northern European markets, and the third scenario assumes that the vaccine is targeting markets with above EU-average Campylobacter prevalence (i.e. mean prevalence about 71.2 per cent).

Shapes of demand curves for Campylobacter vaccine were derived by combining economic margin figures on broiler farms and production quantities in the three scenarios. Hence, a demand price elasticity of -0.69 was estimated for the EU-27 market. The position of the respective vaccine demand curves is calibrated on the assumption that broiler producers face a price reduction, if they deliver Campylobacter-positive birds. Inspired by a Danish example, it seems realistic to assume a price reduction of 1.5 eurocents per broiler, if the flock is positive.

The EU-27 scenario suggests that 356 million doses of vaccine could be sold every year, which adds up to 3.6 billion doses over a 10-year production horizon. The net present value (NPV) of these sales is calculated to 42 million €, taking into account an assumed development period of 7 years and a production horizon of 10 years.

The decision tree framework applied in this study enables economic calculations of Campylobacter vaccine production from different perspectives, including a "direct" and a "probabilistic" perspective. In the "direct" strategy/perspective, the calculated net present value of the project, as evaluated prior to the R&D stage, is 5.9 million €. The NPV increases as we proceed along the process, because the (sunk) costs of the intermediate stages have been laid behind. This perspective could be considered as an "optimistic" perspective. In the "probabilistic" strategy/perspective, we calculate the NPV at different stages in the development process under the assumption that the project has been successful so far (i.e. failures in previous stages are treated as sunk costs), but that there is risk related to decisions and outcomes in the subsequent stages. This perspective could be considered as a "pessimistic" perspective. From this perspective, the expected value becomes positive only after successful completion of the patenting phase.

The economic outcome of the "EU-27" and "HighPrev" scenarios appear to be quite similar, which may reflect a higher profitability (and hence a higher economic ability to vaccinate) in broiler production in some of the member states with high Campylobacter prevalence, implying that these countries are also dominating the demand in the "EU-27" scenario. Demand for the vaccine in the "NorthEurope" scenario is lower than in the two other scenarios, but not very much lower. In general, the profitability as well as the unit cost of the vaccine is not dramatically different between the three scenarios.

Real Option Valuation

The commercial success of new vaccines is highly dependent on research and development (R&D) activities which are complex, dynamic and uncertain. Therefore, it is an important managerial decision to dynamically allocate resources to the most scientifically and financially sound projects. Three main features are typically associated with R&D activities:

- Irreversibility of investment expenditures
- Uncertainty about the future cash flows of the project

- Timing of the project investments

Thus, when it is decided to invest in the development of a new pharmaceutical product, it is not known if a new marketable product will come out at the end of the project. The opportunities and risks of R&D investments may be valued through real options valuations. There are several approaches to estimate the value of real options. Valuation models based on the Black-Scholes and the lattice, especially the binomial-lattice model, approaches are among the most well-known and most utilized in both theoretical and real world applications. These modelling approaches may also be integrated with other quantitative methods.

Similar to a probabilistic approach, valuation of a Campylobacter vaccine development project is also based on a decision tree framework in real options valuation. But eh options approach assumes that the decision maker can opt out of unfavorable choices (for example with negative pay-off). Hence, the outcome of the real options valuation lies between the above-mentioned "optimistic" and "pessimistic" valuations. With the assumptions applied in the analysis, the present value of the vaccine development project becomes significantly positive after successful implementation of the R&D phase, when using the real options valuation method. If we further take into account options to sell the vaccine candidate at different stages of the development process, the expected present value is improved further and can now be positive even before initiation of the R&D phase.

Conclusions and perspectives

The cost analyses in this report suggest that the development, production and marketing of a Campylobacter vaccine involves significant costs, and these costs should be covered one way or the other, if the use of such a vaccine should be common in broiler production. As European broiler production is in general faced with rather fierce price competition, the estimated cost per dose of vaccine is considered to exceed the economic ability of broiler farms to take on this additional cost to vaccinate the birds, unless they get compensated one way or another.

It should however be noted that the cost analyses are based on a number of assumptions, of which some can be considered as rather uncertain. In particular, cost data related to manufacturing and distribution of such products are crucial for evaluating the economics of vaccine development and production, but are very difficult to obtain due to competitive concerns of the pharmaceutical industry; and the market potentials for a new Campylobacter vaccine are also estimated with considerable uncertainty. To the extent that the calculations in this report have been too pessimistic with respect to these two elements, the costs of the vaccine may become lower than those estimated in the report. Furthermore, the outcomes of the report's calculations based on probabilistic modelling and valuation of real options are also highly dependent on the applied assumptions of probabilities of success and failure in the different phases. In our calculations, especially the assumption of an expected 20% success rate in a new R&D project, and the assumption of an expected 20% success rate in clinical testing are critical, and higher expected success rates in these stages will improve the economy of the project considerably.

In relation to decision making, the considerable sensitivity of results to these factors suggests a considerable uncertainty in the quantitative estimates to be derived from analyses such as the one presented in this report. Nevertheless, the quantitative calculations illustrate the importance of different factors, and some relative magnitudes of the costs in different phases, which are important determinants for decision making in business management in pharmaceutics, as well as in decisions regarding public policy, including agricultural policy and health policy.

Marketing a Campylobacter vaccine for broiler production has mainly implications for the pharmaceutical and biotechnology industry, for veterinarians and for the agricultural sector, which are all driven by concerns for economic profitability. The combination of a high level of economic risk and relatively low expected return on invested capital in Campylobacter vaccine development suggests that firms' economic incentives to undertake such investments would a priori be expected to be relatively weak, unless a vaccine candidate of high quality (in terms of expected success rates or market potentials) is identified.

But although the economic incentives to undertake investments in the development of a Campylobacter vaccine may be relatively limited from a business economic perspective, society can still have an interest in such a vaccine, because it can prevent the spreading of Campylobacter from animals to humans, and thus save costs for society, for example in terms of productivity losses or health care costs. Such reductions in the cost of illness could be considered as an external benefit. Hence, the development of vaccines to enhance the food safety might possibly be supported by the public society, if the political decision is to reduce the health cost regarding e.g. Campylobacter. Furthermore, society may have an incentive to support such projects, if they contribute to maintaining and expanding society's research and development capacity, e.g. within the field of microbiological food safety and combat of zoonoses, or within other areas with larger long-run prospects for economy, public health, etc.

Despite the overall potential for vaccines as a cost-effective technology, the pharmaceutical companies have in general only low investments in the development of new vaccines, because they do not reap the external benefits of improved public health (or only a small share of this benefit). A policy implication of this situation could be that a Campylobacter vaccination programme should be supported by the government, for example by subsidizing the investment in research to develop such vaccines, or by subsidizing the running costs of vaccination at the farm level, for example to distribute the vaccine to slaughter companies at a subsidized price, for them to distribute to the farmers with a requirement to use the vaccine. However, for such a public intervention to be successful, it is crucial that a vaccine can be developed at a cost that does not exceed the benefits, including the externality benefits, to be derived from the vaccine.

1. Introduction

Campylobacter *jejuni* stemming from poultry meat is an important cause of food-borne infections, leading to diarrhoea, stomach pain and cramping. Several types of interventions have been suggested to reduce the occurrence of Campylobacter in broiler production. Vaccination of the chicken is one such type of intervention, which is relatively new, and which has thus had modest attention in the literature.

The purpose of the present report is to investigate the costs of developing, producing and marketing a Campylobacter vaccine to be applied in broiler production, taking into account the range of uncertainties involved in these stages, and to evaluate the suitability of alternative analytical approaches to such cost analysis.

1.1. Background

Total and per capita consumption of chicken meat has grown strongly during the last several decades as a result of changing food preferences, increasing household income and population growth. Poultry is expected to become the largest meat sector in the decade towards 2021, according to projections from OECD (OECD, 2012). At a global level poultry products have been said to be one of the world's most valuable animal protein productions, especially because it is produced with higher feeding efficiency and at a faster rate than pork and beef production (Smil, 2002).

Campylobacter *jejuni* is one of the most important causes of socalled food-borne human bacterial gastroenteritis, i.e. Campylobacter causing a combination of diarrhoea and stomach pain and cramping (Els *et al.*, 2007). The incubation period in humans averages from two to five days (EFSA, 2013). According to the European Food Safety Authority (EFSA) this disease is the most frequently reported food-borne illness in the European Union (EU) with more than 150,000 human cases annually, most often from poultry but also found in pigs and cattle (EFSA, 2005). However, the actual number of cases is assumed to be about nine million every year. The cost of campylobacteriosis to the public health systems and to the loss of productivity in EU is estimated by EFSA in 2011 to be about EUR 2.4 billion a year. The EU trend in confirmed cases of campylobacteriosis has shown a statistically significant ($p<0.001$) increase in the period from 2008 to 2011.

Most human cases of Campylobacter infections are associated with consumption of poultry products. Since poultry is becoming more important the strategies to control Campylobacter in poultry products have large political attention in the area of consumers' food safety because of the animal to human disease transmission. However, the proportions of Campylobacter-positive broiler meat samples (single or batch) vary widely among the EU member states with the prevalence ranging from 3.2 to 84.6 per cent in 2011 (EFSA, 2013).

In 2012 the Danish Ministry of Health (SSI) registered 3,722 cases of Campylobacter jejuni/C. coli infections. The real number is assumed to be about 10 to 20 times larger (SSI, 2013), because only a

fraction is reported and diagnosed. The Danish Veterinary and Food Administration (DVFA) made a case by case report that tested fresh chicken meat from Denmark and Europe. The findings showed that 19.7 per cent of the 122 consignments tested in Denmark contained Campylobacter, while it was 44.8 per cent of the 116 surveyed EU parties (DVFA, 2013).

Contamination is possible from farm to fork and requires prevention and control throughout the whole food chain. Some well-known and hypothesised factors having an impact on the epidemiology of human campylobacteriosis include handling, preparation and consumption of broiler meat, which may account for 20 to 30 per cent of human cases of campylobacteriosis, while 50 to 80 per cent may be attributed to the chicken reservoir as a whole (EFSA, 2010).

Another aspect of the Campylobacter bacteria is the seasonal differences in prevalence that can be detected. Campylobacter infections are in most cases isolated events implying that only a single person gets sick unlike the cases of Salmonella bacteria. The risk of becoming sick is greater during the summer (May-September) than in winter time (October-April). In general, the climate has an impact on the higher prevalence risk during the summer compared to the winter period in Northern European countries (Sommer & Heuer, 2007). Furthermore, contaminated water has been demonstrated to be a source of infection for poultry flocks (Sommer & Heuer, 2007). Also the presence of livestock on broiler farms has been considered as a risk factor in infection of flocks with Campylobacter (Sommer & Heuer, 2007). The unintended mechanical spread of bacteria from cattle resident on a farm to successive broiler flocks by e.g. farm personnel, wild birds, vermin, insects (houseflies and beetles), rodents and pets is possible in the absence of appropriate biosecurity procedures and facilities (Sommer & Heuer, 2007). In contrast, feed is not considered as a source of infection due to the low moisture content and because broiler feed is generally subjected to pasteurisation temperatures which are expected to destroy Campylobacter jejuni (Sommer & Heuer, 2007).

At the farm level, Campylobacter bacteria have no direct influence on animal welfare or productivity since the birds live normally even though they may be infected (Shane, 2000). Furthermore, the bacteria from infected birds cause only human health problems if the meat is not handled properly during the slaughter process or cooked sufficiently. The largest risk arises from fresh chicken meat that has not been frozen. Campylobacter is present in fresh chicken meat because many live birds carry the bacteria in the bowels, and the meat is contaminated by the poultry's intestinal contents during the slaughter process. Campylobacter is not possible to annihilate because the live chickens are typically infected from the surrounding environment by flies and other insects, rodents, wild birds, drinking water or even dirty boots when staff moves among the birds. Furthermore, when Campylobacter is entered in a flock of birds then the bacteria spreads very quickly under the right conditions (Rosenquist et al., 2009). The frequency in positive poultry flocks may vary depending on the specific continent and climate zone, and there is typically a strong seasonality in the infection rate. The dynamics of the seasonality are also strongly dependent on the specific region. Northern European countries, for

example, have much sharper peaks of incidence compared to the southern countries (Wagenaar, Mevius & Havelaar, 2006).

Until now, the EU has adopted an integrated approach regarding food safety from farm to fork with the overall goal to protect the consumers from the food-borne zoonoses. This integrated approach consists both of risk assessment and management measures involving all key actors. Furthermore, this approach is complemented with timely and effective risk communication activities (EFSA, 2010). There exist already numerous intervention methods for reducing the Campylobacter in broiler chickens and broiler meat both on farm level and during the slaughter process. At farm level, the following technical methods have been investigated in a recent study of the costs of interventions against Campylobacter in the Danish broiler supply chain: Rodent control, grow-out house standard, fly-screen for grow-out houses, feeding strategy and change in rearing duration (Lawson, Jensen & Lund, 2009). At the slaughterhouse stage the following interventions were analysed in the Danish cost study: Extensive additional washing of broilers, steam-ultrasound, trisodium acid decontamination, crust freezing, marinating and scheduling (Lawson, Jensen & Lund, 2009).

However, the epidemiological characteristics of Campylobacter and the cost-effectiveness of existing interventions methods provide the reasons to postulate that an effective vaccination strategy for infected poultry flocks may be the most effective means of preventing the human diseases from Campylobacter. Experimental vaccines mainly based on killed whole cell cultures have been tested in poultry but provide only partial protection against Campylobacter. Therefore, the development of a weakened live strain may be more promising although not yet commercially available (Els et al., 2007).

A dilemma occurs especially in the organic poultry production that requires extraordinarily good animal welfare. On the one hand rules of organic production require outdoor access for the birds but this cannot easily be combined with high food safety. The consequence is typically a higher zoonotic prevalence on organic poultry farms compared to non-organic farms. Poultry meat from organic flocks contains typically twice as often Campylobacter as meat from the conventional broiler production, but because the organic poultry production and consumption are very marginal, it is believed that the meat only contributes to human illness to a limited extent (Rosenquist et al., 2009).Thus, the dilemma is the trade-off between good animal welfare on the one hand and the acceptance of higher frequency of Campylobacter risk and lower food safety for the consumer on the other hand. A possible solution could be decontamination by freezing or better hygiene in food preparation, but vaccination might also constitute a solution.

1.2. Economic benefits of a Campylobacter risk reduction

Reduction of Campylobacter risk leads to a range of benefits, of which some can be characterised as market – or private – benefits, and some can be considered as non-market – public good or externality – benefits. These benefits are reviewed in the following.

1.2.1. Valuation of market benefits

From a business perspective, private benefits from reducing the prevalence of pathogens may include improvements in shelf life, retention of existing customers, access to new (e.g. export) markets, decreased scrap or reworking of products and reduced product liability (Jensen & Unnevehr, 2000). Furthermore, from a consumer perspective, benefits from reduced pathogen risks may include reduced costs of averting contaminated foods and higher product confidence.

Improved microbiological safety of food products can be expected to increase the market value of the products by different mechanisms. Consumers may exhibit a higher willingness to pay for food products with lower Campylobacter risk, and this willingness to pay may be transmitted backwards in the food supply chain, thus also implying a higher value of Campylobacter-free poultry products from the farmer. But processors and/or retailers may also valuate a lower risk of food crises positively, for example a lower risk of major human Campylobacter infection outbreaks, with associated reputational losses and drops in the demand for their products or liability costs.

During the last couple of decades, substantial efforts have been devoted to quantifying consumers' willingness to pay for product attributes such as high food safety. A number of methodological approaches have been developed, some based on the revelation of consumers' preferences via their market behaviour, and others based on consumers' direct statements about their preferences or willingness to pay.

Valuation of benefits through *market prices* relies on the differences between prices paid in markets for products with different safety attributes, using hedonic techniques (i.e. interpretation of price differences as premium for differences in risk) or by techniques based on people's averting behaviour. In a study by Jensen et al. (2004) based on sales data from one of the largest retail chains in Denmark (Coop) in 2000-2002, the willingness to pay extra for Campylobacter-free broilers was estimated to be between 2 and 8 DKK per kg (corresponding to between 0.15 and 1.10 € per kg), depending on the volume (with a lower extra WTP, the larger the volume to be demanded).

Direct willingness-to-pay approaches use consumers' statements about their willingness to pay for lower health risk in general or for specific safety attributes in foods, or stated choices or rankings of products with different (e.g. food safety) characteristics. Such studies may rely on open-ended questions about the willingness to pay (e.g. contingent valuation methods), but in recent years methodologies using real or virtual choice experiment data have been developed, where test persons are asked to choose between commodity varieties with different levels of e.g. food safety, price and possibly other attributes, and where these choices can be analysed statistically. Examples of this approach include Christensen et al. (2006), who use virtual choice experiments to reveal consumers' willingness to pay for labeling of Campylobacter-free broilers (around 2.75 € per broiler) and their trade-off between food safety and animal welfare, and Mørkbak et al. (2011a) who estimate a willingness to pay for "Campylobacter-free" labelling of 3.00-3.40 € per 500 grams. Hayes et al.

(1995) used real choice experiments to explore the willingness to pay for safer food and found that on average willingness to pay for safer food is approximately 0.70 US$ per meal. Another – more qualitative - methodology for analysing consumer preferences is c*onjoint analysis*, where respondents' ranking of various combinations of attributes is used to determine preferences and trade-off dilemmas of the respondents. For example, Meuwissen and van der Lans (2005) apply customized conjoint analysis on Dutch pork consumers' trade-offs between food safety and other quality attributes, finding that food safety and animal welfare are the most important to consumers, together with taste and price.

The amount of research addressing the value for food industry and retailing of avoided reputational losses or liability costs, where benefits are measured in terms of the avoidable costs for parties in product liability cases, is relatively scarce. Some studies have been made in relation to the BSE crisis in the mid-1990's, (Lloyd et al., 2001; Mazzocchi, 2000) and for Salmonella in eggs (Smed & Jensen, 2005), showing significant changes in demand behaviour (of which some are temporary and some may be more permanent), which may have serious implications for profitability in the respective food supply chains, but the authors are not aware of any such studies in the field addressing Campylobacter. As pointed out by Caswell (1998), data on actual costs of liability will often be hard to obtain because a significant share of cases are settled out-of-court.

As mentioned above, end-user benefits of improved food safety may imply a higher willingness to pay for the products at the consumer stage. This willingness to pay can be translated to a farm price premium via backward price transmission, for example to calculate the maximum price on the market that the producer can cover for reducing Campylobacter risk, and hence how much is available to cover the development and production costs of e.g. a vaccine.

Despite the positive attitudes towards reducing food risks, consumers are skeptical towards some of the methods for improving microbiological food safety, such as mechanical decontamination (hot water, steam) or chemical treatment of meat products (Korzen & Lassen, 2010; Mørkbak et al., 2011b). Indeed, consumers' willingness to pay for risk reduction resulting from mechanical decontamination is offset by their negative willingness to pay for the use of this risk reduction method. There is however no evidence, whether such skepticism would also apply with regard to broiler vaccination, but the decontamination example illustrates that there might not be societal acceptability of using some of the risk reduction strategies that seem promising from an industry point of view.

Currently, Danish poultry processing companies make a deduction in the prices paid to broiler farmers, if the delivery is Campylobacter positive (about 0.01 € per kg), and a further deduction if the delivery is Salmonella positive (0.02-0.04 € per kg). Furthermore, the processor may pay a premium for complying with specified hygienic standards on the broiler farm.

1.2.2. Valuation of non-market benefits

In addition to market benefits, there may also be benefits of a more 'public good' or 'externality' nature, which do not yield direct benefits to the consumer, and hence does not provide an incentive to

pay a higher price for the product, but nevertheless yields cost savings or benefits for other parties in society. Examples are saved health care costs or reduced absenteeism from work due to lower disease risk[1].

The dominating approach to estimating non-market benefits related to food safety is the human capital – or Cost of Illness - approach, where benefits in terms of reduced health risk is measured in terms of the gained expected lifetime earnings and activities. The *Cost of Illness (COI)* approach measures the benefits of an improvement (e.g. improved food safety) by the value of avoided illnesses, deaths, losses in income and leisure, pain and suffering (Caswell, 1998). The use of the COI approach within the field of food safety has been developed by Roberts (1989). Whereas other measures of disease burden (Disability Adjusted Life Years – DALY - or Quality Adjusted Life Years – QALY) evaluate impacts on mortality and morbidity in terms of change in number of years[2], the COI method evaluates the effects of interventions on disease burden in monetary terms as changes in medical costs and productivity loss. In the particular case of *Campylobacter* risks, such costs are assumed to include health care costs related to individuals with a diagnosis of campylobacteriosis (of which a share are serious requiring substantial treatment, e.g. hospitalization, whereas others are settled after one consultation with the practitioner) and disease-related productivity losses. It is estimated that the average cost is 1,850 € per incidence[3]. It has been estimated that the mortality rate of the registered cases of campylobacteriosis is 0.5 per cent, which implies that out of around 3,000 registered cases of campylobacteriosis, around 15 persons can be expected to die as a direct consequence of their infections. The value of life savings is however not included in the cost of illness estimate, so the 1,850 € could be considered as a lower-end estimate of the benefit. A previous unpublished paper by Jensen et al. (2011) suggests that the benefit – in terms of saved COI - associated with reducing the Campylobacter risk by 75 per cent amounts to about 1.5 eurocents per broiler.

Various alternative approaches to the valuation of the disease burden and disease risks have been reviewed and discussed by Kenkel (2001). The COI approach has been applied in a number of studies regarding pathogen-related food safety, including Buzby et al. (1996), Crutchfield et al. (1997), Roberts et al. (1996) and Korsgaard et al. (2005). Although the studies share the basic COI approach as a point of departure, they also differ in various aspects. For instance, some studies include the value of deaths, whereas other studies don't. Buzby et al. (1996) is a key reference with regard to the quantification of disease costs from bacterial foodborne diseases. The study provides a detailed analysis of the risk of

[1] It should however be mentioned that the above approaches to estimating benefits do not *per se* ensure that these benefit estimates are exclusively private benefits.
[2] Mauskopf & Morales (2001) provide a review of such studies, distinguishing between "top-down" (based on aggregate information about number of disease cases) and "bottom-up" studies (based on estimates of exposures and dose-response relationships). Furthermore, Mauskopf & Morales develop a method for combining different health outcomes into an aggregate QALY measure.
[3] It is assumed that a person is absent from work for 6 days on average and 17 per cent of the persons registered with campylobacterioris are hospitalized (Korsgaard et al., 2005). The prices have been extrapolated from 2001 to 2006 using a 2 per cent inflation rate.

acute and permanent disease problems or deaths caused by infection of various pathogens, including Salmonella, Campylobacter, E.coli and Listeria, and associates treatment costs with these diseases and a value of statistical life to deaths. This study has formed the basis for many of the subsequent evaluations of food safety enhancing interventions in the United States, including Roberts et al. (1996), Crutchfield et al. (1997), Golan et al. (2000) and Goodwin & Shiptsova (2002). Mangen et al. (2005) provide a COI study of Campylobacter in the Netherlands, whereas Korsgaard et al. (2005) (cited in Andersen and Christensen, 2004) provide a Danish COI study of Salmonella, however not including the death risk.

Table 1.1: COI benefit estimates of reduced pathogen incidences

Reference	Disease	Country	Cost estimate
Buzby et al. (1996)	Salmonellosis	US	908 1993-US$/ incident
Buzby et al. (1996)	Campylobacteriosis	US	468-550 1993-US$/ incident
Buzby et al (1996)	E.coli	US	15.000-18.000 1993 US$/ incident
Buzby et al. (1996)	Listeriosis	US	63.000-69.000 1993-US$/ incident
Korsgaard et al. (2005)	Salmonellosis	DK	671 DKK/ incident
Mangen et al. (2005)	Campylobacteriosis	NL	255€/incident

Cost-of-illness estimates as illustrated in Table 1.1 may be considered as a lower-bound estimate of benefits, because they do not include averting and avoidance costs (Van Ravenswaay & Hoehn, 1996). This is supported by Kenkel (2001) who finds considerably higher estimated value of statistical lives (VSL) if they are valued using WTP methods than if studies are based on human capital assessments. On the other hand, COI-estimates include health costs that are not paid by the consumers – costs that would not be captured by valuation studies.

1.2.3. Economic benefits from international trade effects

Taking into account international trade, an effective vaccine improving microbiological food safety can lead to economic welfare gains via its impacts on trade barriers. From the perspective of an individual country, improved food safety can assist in creating access for the country's exporters to high-end markets in other countries. But improved food safety in domestic production can also act as a tool for the country to establish barriers against imports of low-cost but high-risk products, thus yielding some degree of protection of domestic firms against imports.

From a global perspective, however, a higher level of food safety at an international level can also have a general trade creating effect, thus enabling countries to reap the welfare economic benefits arising from higher utilization of comparative advantages and consequently better utilization of countries' resources. In addition, the improved food safety can enhance the availability of resources in terms of lower workforce absenteeism in all the countries experiencing reduced food safety risks (Jensen & Jensen, 2013).

1.3. The development of a new Campylobacter vaccine

Vaccination can be seen as a way to avoid the high costs of a disease and also to enhance food safety to the society. The aim of such vaccination should be to protect the chickens from exposure from an early age, to eliminate colonization by the time of slaughter and/or to reduce the concentration of bacteria in the meat.

A huge number of challenges are associated with the development of a new Campylobacter vaccine for broiler production. The market for veterinary vaccines is limited in size and spread across different types and the development of vaccines becomes more and more complex and expensive over time (O'Brien & Zanker, 2007).

One aspect is the economic attractiveness of a new vaccine investment in general. From the pharmaceutical industry's point of view there is a trade-off between investment in the development of new vaccines and the investment in other new pharmaceuticals, and the expected economic value or payback of the invested capital is assumed to determine what projects are chosen. This crucial decision is also made with respect to the time uncertainty both with regard to the competition on the market and with respect to the nature and stability of the Campylobacter bacteria.

Vaccines are biological agents. Storage is costly and time limited, and adjustment of the productive capacity is slow, costly and governed by regulation. Production is characterized by economies of scale and is subject to large-scale errors (batch failures). As the development of a new vaccine is a lengthy process, only a small fraction of all vaccine candidates are marketed in the end. Reasons for research abandonment may be grouped into different categories, such as safety e.g. human or animal toxicity; efficacy e.g. activity of vaccine too weak or lack of efficacy; and economics e.g. the commercial market too limited or yielding insufficient return on investment.

There are some countervailing arguments in the development of vaccines: Anticipated profits drive innovation. Thus, higher prices on vaccines increase profits and thus the incentives to innovate new vaccines. Therefore, taking steps to lower prices today reduces the incentives of developing drugs and vaccines for tomorrow. On the other hand, high prices above the production costs foreclose the market for specific consumer groups or eventually entire countries with low purchasing power.

In summary, the development and manufacturing process, including researching, testing, gaining regulatory approval and manufacturing vaccines are costly, complex and lengthy. Vaccines are biological products that have to meet specific, extensive regulatory requirements throughout their development, production and distribution cycles. Finkelstein (2002) concludes that the time lag between initiation of successful clinical trials of vaccines and licensure are about the same (6-8 years) as for other drugs and that the success rate of clinical trials is somewhat higher.

1.3.1. The cost structure of a new vaccine

Estimating the costs of developing, testing, producing and launching a new vaccine involve several challenges. A way to estimate the cost of developing a vaccine is to use benchmark data from the industry. The development of a new product may take from eight to ten years (O'Brien & Zanker, 2007). Overall, most if not all new vaccine products have to demonstrate safety, quality and effectiveness, so that they finally can be approved by the authorities before the launching.

Like the period varies, so does the cost of this development process, but a rough estimate indicates the cost on average is US$ 50 million (O'Brien & Zanker, 2007). Other estimates have come out higher. Thus, evidence from vaccines used for humans indicate that research and development costs for vaccines can exceed US$ 800 million and that the development process may require 10 years or more. Strict manufacturing regulations and facility upgrades add to these costs (Muzumdar & Cline, 2009). Because of the competition, the veterinary pharmaceutical industry is however not very likely to share information about their specific development costs (Madsen, 2012). Over time the implemented technology is becoming still more advanced and therefore the regulatory requirements also become complex, leading to even higher costs of developing a new vaccine. On the other hand, however, new technologies may also speed up the process and save time and costs in the long run. Commercial vaccine development and production will typically only be undertaken if the vaccine sales can be expected to cover both the development and production costs and also provide some profit to the owners of the pharmaceutical firm.

Evidence shows that the fixed costs reach up to 90 per cent of total production costs, when dealing with vaccines used for humans (GAVI, 2004). Although this cost is not exactly comparable to veterinary vaccines, the different cost components are still relevant. These fixed cost components include research and development, patent costs, quality control and quality assurance as well as the costs of clinical trials and secondly trials in poultry flocks at different locations. Vaccine production costs per unit can be reduced significantly through gains in productivity, known as the "learning curve" and through economies of scale and scope. Due to the relatively high fixed cost component, the cost of production per dose decreases with increasing batch size.

The specific cost of production depends on the type and technological characteristics of the developed vaccine. The vaccine production technology basically consists of three different types. Live vaccines (lentogenic vaccines and heat tolerant vaccines) are cheap. The inactivated vaccines are more expensive, compared to the live vaccines, and also more difficult to apply (FAO, 2004). Finally, the recombinant vaccine (DNA) is very expensive to produce. Depending on the type of vaccine technology, the production cost of the vaccine is expected to determine the sales price to the farmer. Also additional farm costs, such as the vaccine delivery methods are crucial to take into consideration. In general, mass administration methods like via drinking water or via feed are already used for other vaccines, but possibly a new vaccine requires various forms of equipment and also start up consultancy (Marangon & Busani, 2006).

1.3.2. The pricing of vaccines

Vaccines are widely applied in all the various poultry producing systems. The global biological markets for these species accounted for total sales of US$ 585 million in 2002, which were almost equally divided between live (45 per cent) and inactivated (55 per cent) vaccines stated by Wood & MacKenzie (unpublished data) (Muzumdar & Cline, 2009). Today, the development and especially the launch of vaccines are becoming big business. The major producers of animal vaccines are divisions of global pharmaceutical companies.

It is in general assumed that new vaccines carry higher prices compared to older, and widely used, vaccines. The reason for this is that the fixed costs of production of old vaccines have been covered long ago and because the production costs have been lowered due to the learning curve and economies of scale. For new vaccines the high fixed costs and steep learning curve cause more expensive vaccines as the investment in R&D and production facilities need to be paid off and optimum production techniques need to be perfected to reduce variable production costs. New vaccines that involve recombinant DNA technology may not be as feasible to large-scale production as vaccines produced by more traditional techniques. Therefore, the prices for these advanced vaccines may never reach the same low level as the traditional vaccines (GAVI, 2004).

The challenge of bringing new animal vaccines to the markets and to obtain a profitable return on the investments is dependent on an effective management of the product life cycle in a way that both the producers and the customers will benefit. One model of the product life cycle for vaccines is shown in Table 1.2. The product life cycle in the table has three distinct phases: New Product Launch, Market Penetration and Product Maturity. One important way to optimize the supply and profitability of new vaccines is through systematic price tiering across markets as shown in the last column of Table 1.2. Price tiering may be possible due to price discrimination, scale sensitive manufacturing economics and distinct product life cycles.

On launch there are normally just one or a few producers who have the intellectual property rights of the vaccine and sell the product in the markets. This phase is generally characterised by low capacity, high production costs and high market prices. The market penetration phase is characterised by the entrance of new producers – their entrance strategy may be based on their own development efforts or e.g. licensing – implying that the production capacity and thus supply of the vaccine will increase. In the product maturity phase the intellectual property right of the product has typically expired implying that there may become many suppliers of the vaccine. In this stage, production costs are typically low due to excess capacity which may be counteracted by price tiering among the vaccine producers.

Table 1.2: Managing the product life cycle (adapted from Mercer Management Consulting, 1997)

Factor	New product Launch	Market Penetration	Product Maturity	Optimal Situation
Number of producers	One of few	Several producers in high income countries	Several producers in both high income and developing countries	
Pricing	High, uniform		Tiered within and across markets (global): low average price	Tiered within and across markets (global): low average price
Cost	High	Medium	Low	Low
Profitability	Uncertain	High	Low	Uncertain
Capacity	Low	High	Surplus	High
Vaccine availability	Poor	Good in high income countries	Good world-wide	Good world-wide
Market demand	Low	High demand in high income countries and the private sector of lower income countries	High world-wide	High world-wide

Source: GAVI (2004).

1.4. Organisation of the report

The remaining parts of the report are organised as follows. Chapter 2 provides a rather detailed systems analysis of each of the phases in development and launch of a new Campylobacter vaccine to be used in the broiler production. The aim of the analysis is to identify the main decisions and potential outcomes in each phase of the development and marketing process.

Chapter 3 contains a description of the assumptions adopted to estimate the costs and revenues associated with the development and marketing of the Campylobacter vaccine. Cost assumptions are made from a wide number of different sources whereas the expected revenues mainly estimated on the basis of statistics from Eurostat and information published by different EU institutions. The chosen cost and revenue assumptions form the basis for calculating the expected net present value of the investments in a new Campylobacter vaccine.

Real option valuation methods are presented and utilized in Chapter 4 in order to analyse the uncertainties associated with the development and marketing of a new Campylobacter vaccine and to evaluate the economic consequences of these uncertainties. The motivation for adopting this methodology is that the traditional discounted cash flow and net present value methods are incapable of valuing the flexibility arising from the volatility of the associated technical and market conditions. As shown in this chapter, the obtained results may differ significantly from the results obtained by using the conventional investment appraisal methods.

Chapter 5 summarizes the main conclusions derived from the performed analyses and discusses some perspectives for the pharmaceutical industry, policy-making and the research and development community, respectively.

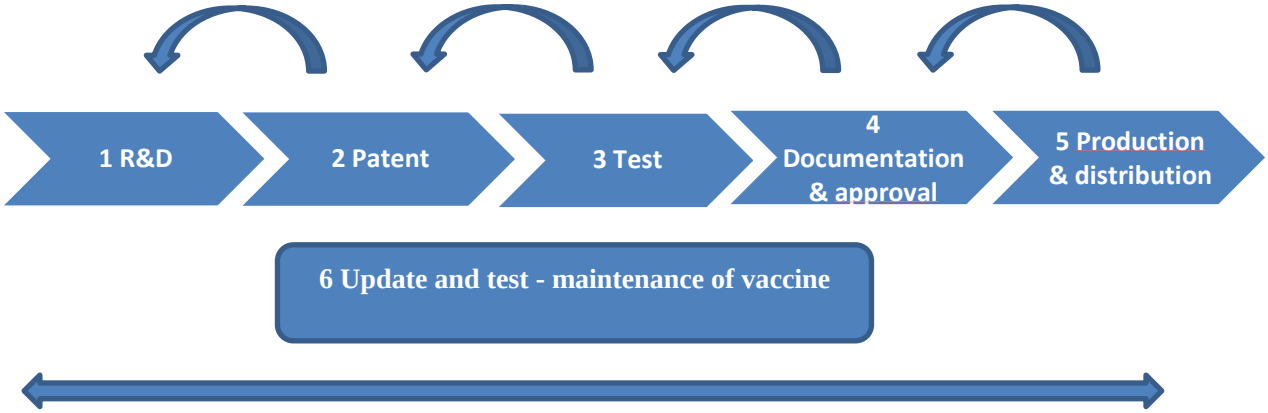
2. Systems analysis of the development and launch of a new Campylobacter vaccine

Biotechnology firms are facing major markets and private risks in the development and launch of new vaccines and drugs in general. Market risks relate to e.g. the size and scope of the market, regulatory issues, consumer expectations and pricing, intellectual property rights (IPR) as well as competition trough generic and copy products. Private risks include technological risks such as technical feasibility and failure risks as well as financial, organisational and managerial risks. In this chapter a systems approach is adopted to identify and evaluate the effects of this complexity of risks and their associated relationships on the costs and benefits related to the development and launch of a new Campylobacter vaccine. The systems analysis is described in sections 2.1 and 2.2, respectively. In the first section, the vaccine development and launch are decomposed into a number of overall stages. In the next section, the decision alternatives and their expected outcomes within each of these stages are identified and described within a decision tree framework.

2.1. Main stages in the development process

From a systems perspective the development and launch of a new Campylobacter vaccine can be decomposed into a number of sequential subsystems. Overall, it is assumed that the development and launch of a new Campylobacter vaccine consists of basically six distinctive phases: (1) Research and development; (2) Patenting; (3) Testing activities; (4) Documentation and approval; (5) Production and distribution of the vaccine; and (6) Further updating and testing activities to maintain the efficacy and safety of the vaccine. The phases are illustrated in Figure 2.1. Two major parts can be distinguished in the staged system model: The part which includes R&D, testing and approval of the new vaccine, i.e. stages 1-4; and a second commercialisation part which includes the development of the large-scale production capacity, the marketing and sale capabilities as well as the maintenance of the vaccine, i.e. stages 5 – 6.

Figure 2.1: Overview of the vaccine development and launch phases



The main components embedded in each of the phases of the development and launch of a new Campylobacter vaccine are shown in Table 2.1. The stages included in the Campylobacter development process are rather similar to the phases that are generally adopted in the development of new drugs and biotechnological products although the sequence of the stages may vary between the development projects.

Table 2.1: Main components in the vaccine development process

	Input	Output	Risks	Cost range	Time range
R&D	Lab facilities Research work Technical work	Vaccine candidates Scientific knowhow White papers	Microbiological difficulties An unstable organism	High	≈3-5 years
Patent	Consulting (lawyer) costs of the patent assessment and legal approval	Intellectual property rights	Application delay Application rejected Application withdrawn	Low	≈1-2 years
Test	Experimental trails (Clinical trials): animal experiments (few birds, fully controlled) Field flock trials on poultry (400-500 birds)	Experimental results Value of new knowledge	The field trails are often the most risky part, many factors influence	Medium	(including field trials) ≈ 2 years
Approval/ Documentation	Administrative costs Approval fees	Documentation of effect and security applications	Extra tests required Unexpected additional costs	Medium	≈1-2 years (with good results)
Production/ Distribution	Variable costs Fixed costs	Marketable vaccine doses Revenues Sales profit	Large scale production problems Lower sale than expected Price	Low	≈1year
Update of vaccine	Lab facilities Research work Trials	Updated vaccine	False positive Positive false	Low	Continuous

The generic stages reported in the scientific literature include (Kellogg & Charnes, 2000; Borissiouk & Pell, 2001): 1. Discovery and preclinical research; 2. Clinical trials which are generally broken down into three sub-phases: Phase I where testing is conducted on a small sample of volunteers to assess drug toxicity, safety etc.; Phase II where the drug is administrated to a large sample of subjects to provide evidence on efficiency and additional safety information; and Phase III testing that includes large scale trials on humans to collect more comprehensive data on efficiency, safety as well as on different types of side effects. 3. After the clinical tests have been completed successfully, documentation of the obtained results is assembled and submitted to governmental agencies for approval. 4. Parallel to the approval phase many biotechnological firms establish the necessary production and marketing facilities to sell the developed drug in selected markets. 5. Very often while the firm generates income from the sale of the new drug, it also conducts further research and development activities to support the marketing activities and if possible development new variants of the drug.

In the following section a decision tree model for each of the first five stages of the Campylobacter vaccine development and launch process is outlined. No decision tree is, however, developed for the final stage (6 update and test - maintenance of vaccine), that is the further testing and update of the vaccine. The reason is that this stage in principle runs parallel with the production and marketing of the vaccine. Thus, during most of the market life cycle the vaccine will be further tested, evaluated and eventually updated to maintain its market value. Therefore, it is implicitly assumed in the model development that the post-testing update stage is included in the production and distribution stage.

2.2. A decision tree representation

Decision trees are one common approach to represent decision problems under uncertainty. A simple decision tree model of the vaccine development and launch phases in Figure 2.1 is illustrated in Figure 2.2. The decision tree model includes in principle four elements (Lander & Shenoy, 1999):

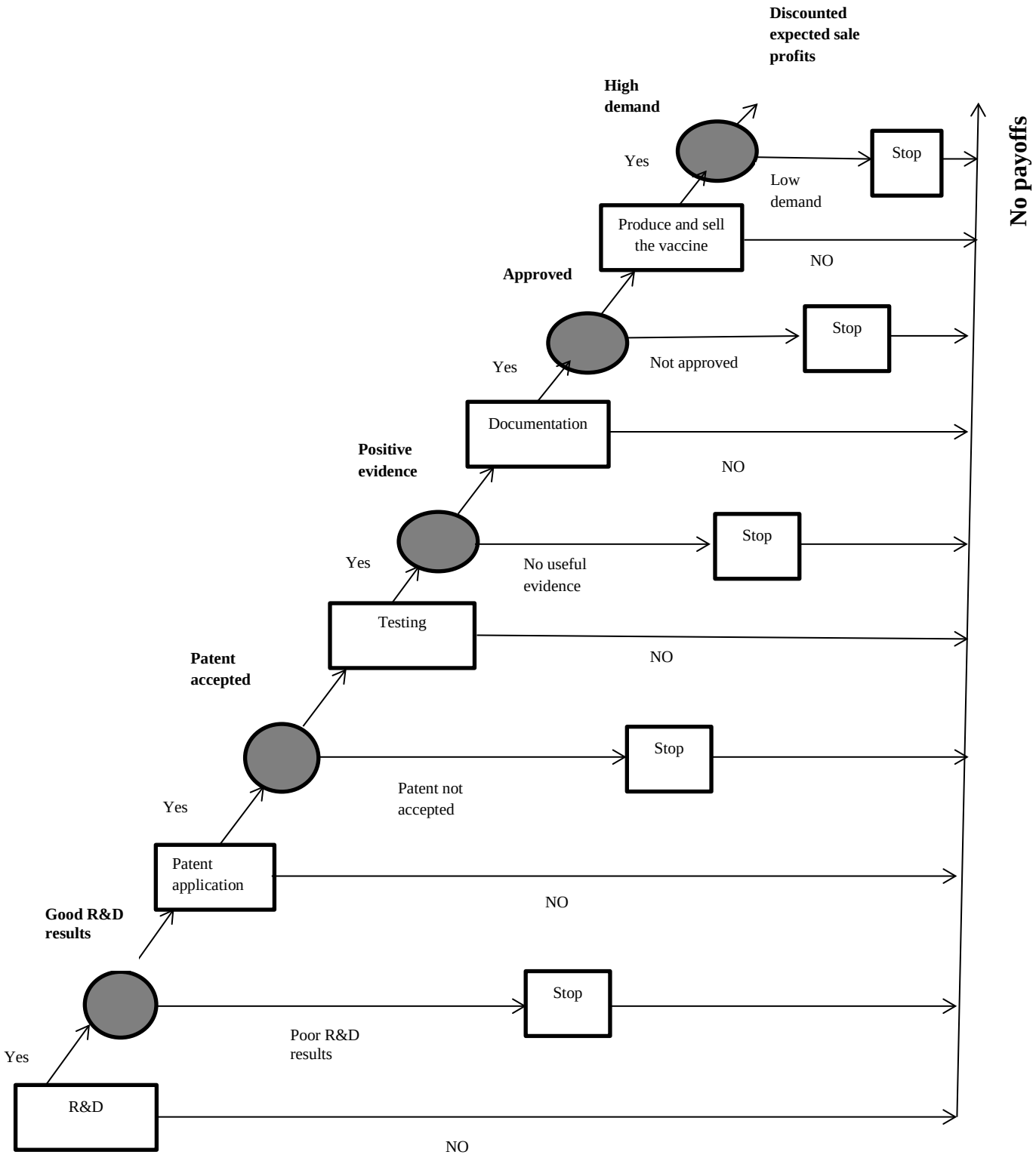
- a sequence of decisions (represented by squares or “decision nodes”)
- uncertain events with a complete probability specification (represented by circles or “chance nodes”)
- the resulting outcomes and the net benefit (cost) or preferences of each possible outcome; and
- the information constraints specifying what uncertain events the decision-maker knows and does not know at each point when a decision has to be made

In a decision tree, all possible scenarios must be included. The decision-maker can choose only one alternative (branch) at a decision node. Branches from a chance node must be mutually exclusive and collective exhaustive. Furthermore, the sequence of decisions in a decision tree glows from the root to the leaves.

In Figure 2.2 the tree begins with the decision to undertake R&D activities in the vaccine candidate. If the decision is “yes”, there is a chance that good R&D results will be obtained and there is also a chance that poor R&D results will be obtained. In the decision tree it is assumed that if poor R&D results are obtained, then it is decided to stop the research project and no payoffs will result.

However, in case of good R&D results the project moves to a new phase where a decision has to be made whether to make a patent application or not. Despite good R&D results it may be decided not to apply for patent, e.g. because such patents already exist. However, if it is decided to apply for patent, the decision tree shows that it is not 100 per cent sure that a patent will be issued. A patent application may not only be denied because of other patents, but also because e.g. the application is not fulfilling all the formal requirements. If the patent is issued the next decision phase in the figure is whether to test the vaccine candidate or not.

Figure 2.2: A simple decision tree for the development of a new vaccine



The tree in Figure 2.2 contains five sequential decision phases where the actual decision in each phase is conditional on the specific decision and its specific outcome in the previous phase. For example, it is decided to stop the project if a test had been decided in the previous phase and the test results indicate that the efficiency of a Campylobacter vaccine is expected to be very low. Thus, when a decision has to be taken, the decision maker already has some information about the results of the previous phases. For example, when the decision to submit a patent application has to be taken, the decision makers are already aware of the research results at the R&D stage. However, this information may not be 100 per cent certain. Hence, the use of these results may be encumbered with errors. For example, although the R&D results are good, there is a probability that the tests will fail to provide any positive evidence of vaccine efficacy (Borissiouk & Peli, 2001).

Although no payoffs, costs, probabilities etc. are included and the information therefore is qualitative, the figure still contains important decision information. First, the tree graphically shows the sequence of events and possible decisions. Second, it also indicates that the value decreases as one goes backward in time toward the beginning from the expected profit in the end of the tree. This is because of the combination of success probabilities (payoff are only carried forward if all subsequent phases are successful and if continuation is chosen in the future) and discounting. Third, the decision tree demonstrates that the analysis already assumes considerable management discretion: at each decision point a choice of go/no go has to be made depending on the expected future payoffs (if they are negative, cancellation is preferable).

The individual stages in the decision tree can be detailed further. The following sub-sections outline such decision trees for R&D, patenting, testing, approval and production/distribution phases, respectively.

2.2.1. Decision tree for R&D

The decision tree for the research and development (R&D) phase is illustrated in Figure 2.3. The figure is read from left to right. The initial state (called the root node) is assumed to be that a new vaccine candidate is available which has already shown some promising, but also very uncertain, evidence of biological efficiency. Furthermore, it is assumed that the project team has to make one of the following decisions:

- invest more R&D into the vaccine candidate
- no additional R&D and no test of the vaccine candidate, i.e. stop the project

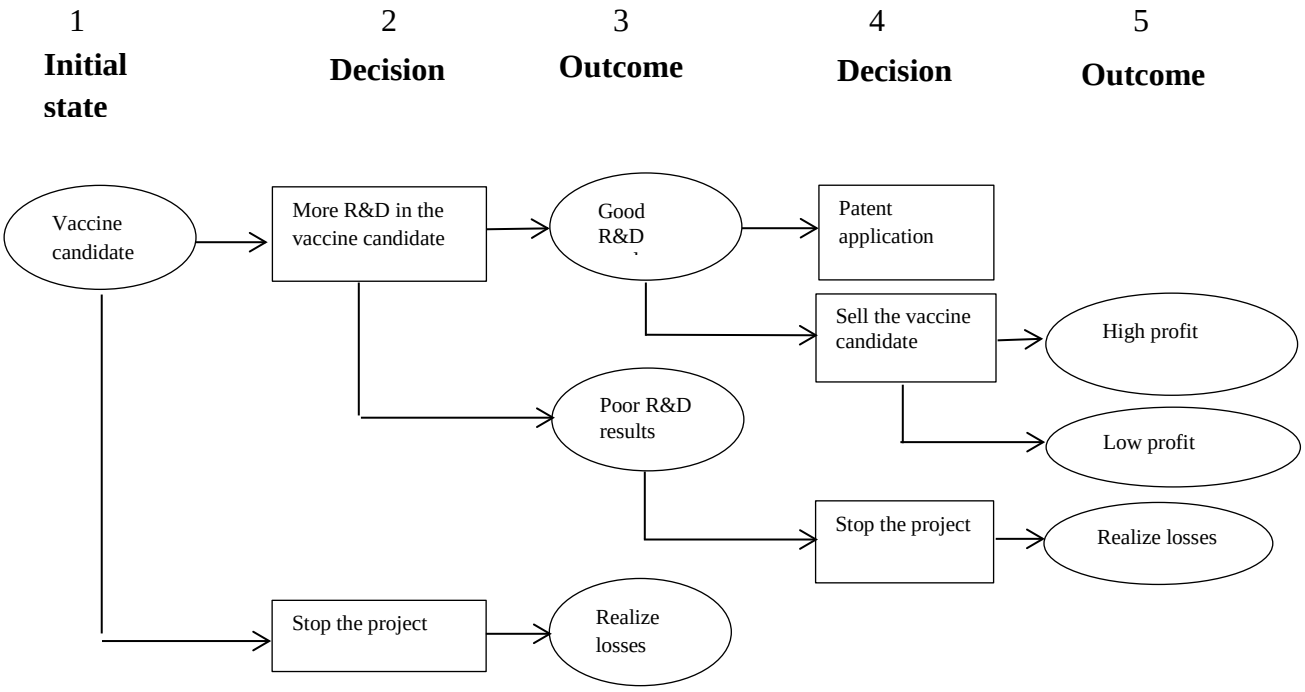


Figure 2.3: Decision tree for the R&D phase

If the decision alternative "Invest more R&D into the vaccine candidate" is chosen, then two different outcome scenarios are assumed possible: "Good R&D results are obtained" or "Poor R&D results are obtained", which also are shown as branches emanating to the right of this decision node.

If the outcome "Good R&D results are obtained" is realized, then two decision alternatives are available: "Make a patent application" or "Sell the vaccine candidate". If the decision alternative "Sell the vaccine candidate" is chosen, then there are two different possible outcomes: A "High profit" or a "Low profit" from the sale as illustrated in Figure 2.3.

However, if the decision alternative "Stop the project" is chosen then there is only one realistic outcome which is that an economic loss will be realized.

2.2.2. Decision tree for patent application

Two outcomes of a submitted patent application are assumed. Either the application is accepted or not accepted. The likely outcomes of the decision to submit a patent application are shown in Figure 2.4.

If the patent application is accepted (i.e. approved) by the relevant patent agency, two decision alternatives are assumed to be available:

- proceed with testing the vaccine candidate; or
- sell the vaccine candidate

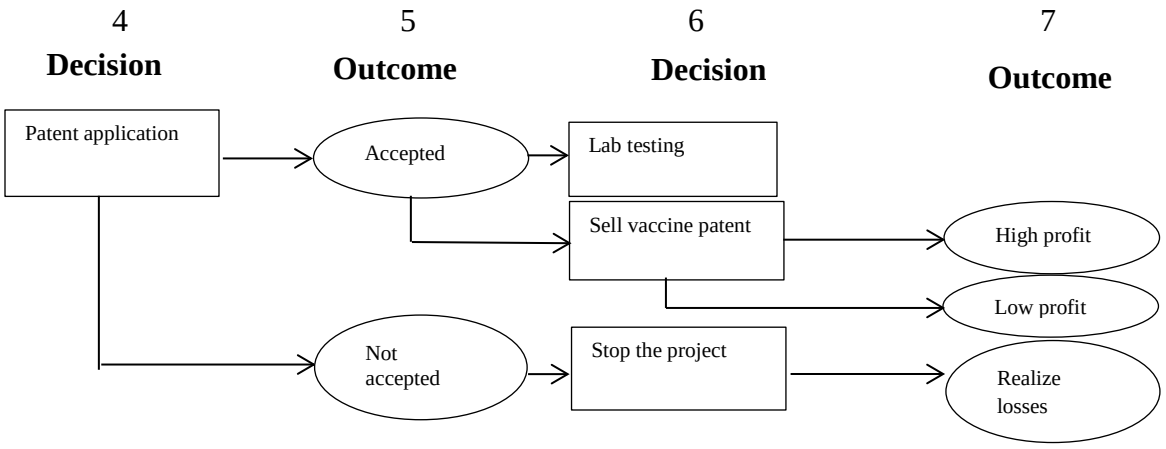


Figure 2.4: Decision tree for the patent application

The expected consequences associated with the decision to go ahead with the testing of the new vaccine candidate are presented in section 2.2.3.

Alternatively, if the decision "Sell the vaccine" is chosen, then there are two different possible outcomes: A "High profit" or a "Low profit" as illustrated in Figure 2.4. If the submitted patent application is not accepted, then only one decision is assumed to be available: stop the project. When the decision "Stop the project" is chosen, an economic loss will be realized.

2.2.3. Decision tree for testing

The assumed decision tree for the testing phase is illustrated in Figure 2.5. It is assumed that the test of the new vaccine candidate includes three separate sequential stages:

- Laboratorial testing
- Subclinical testing in constructed production facilities
- Clinical testing on real poultry farms

Each outcome may lead to different decisions. If no positive evidence is obtained in each of the three testing phases, the project is cancelled and the economic losses are realized. On the other hand, if all the three testing phases lead to positive evidence, we assume that there are two decision alternatives:

- proceed to the documentation/approval phase
- sell the tested vaccine

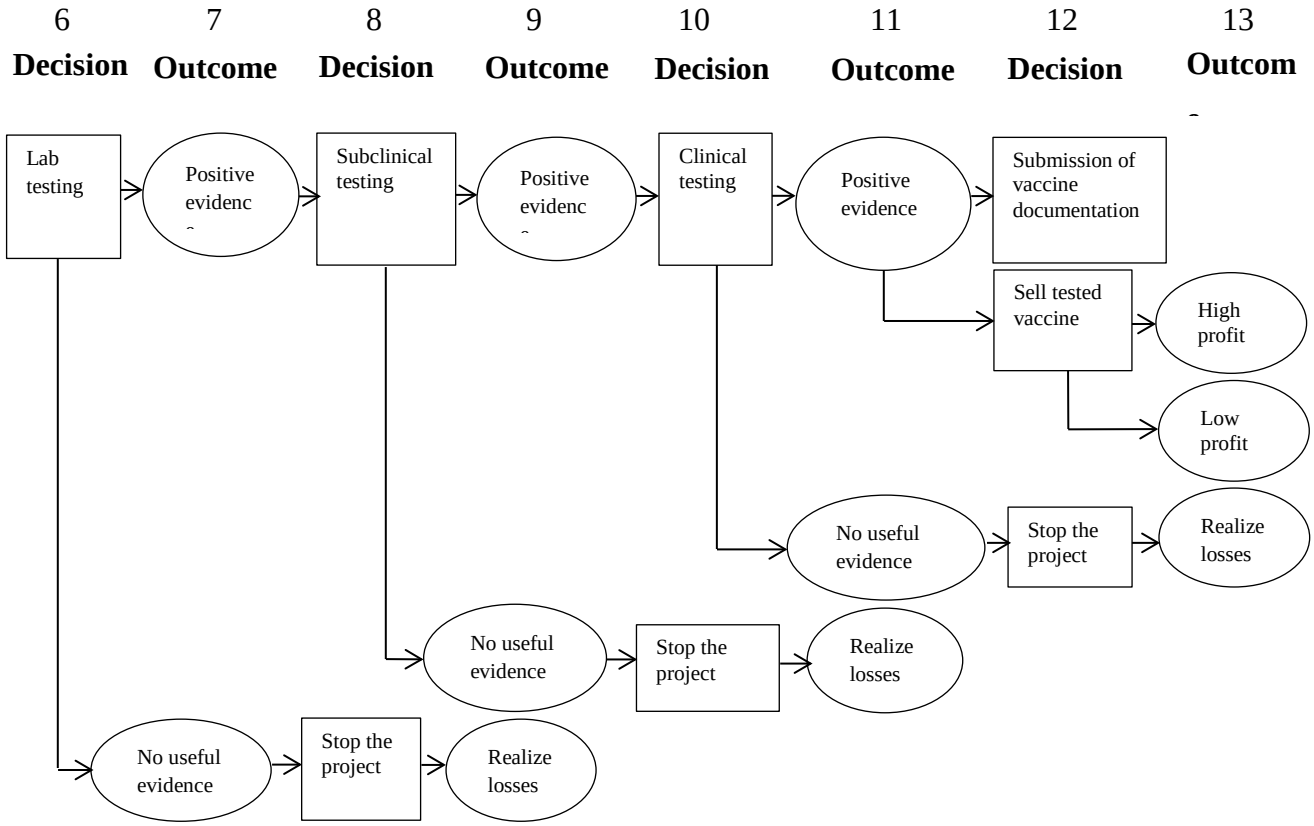


Figure 2.5: Decision tree for the testing phase

Each of these types of decision may have different implications for costs and earning potentials. The specific content of the decisions may depend on the test outcome. The rationale for each of these types of decision – and hence the likelihood of the specific decision taken - naturally depends on the outcome of the tests. If it is decided to sell the tested vaccine either a high or low sales profit may be expected. The likely outcomes of the submission of the vaccine documentation for approval are shown in the following section.

2.2.4. Decision tree for documentation and approval

Approval refers to the marketing authorization of the new vaccine. The documentation used in the application together with the test results and the size of the fee payments determine how the vaccine is approved, and for how many countries it can be marketed. The European Medicines Agency or The Danish Health and Medicines Authority provide the authorization of the new vaccine. Fees also have to be paid before it can be produced and launched.

Approved or not approved are the two only possible outcomes of the submission of the vaccine documentation to the approval authorities (Figure 2.6). If the vaccine is approved, two alternative decisions can be discerned:

- Proceed to perform a market survey (see section 2.2.5)
- Despite the approval, it is decided not to start any production of the vaccine

However, if the vaccine is not approved, it is assumed the project is terminated and the losses are realized. It is assumed that the cost implications are the same whether the project is stopped because of the lack of approval from the authorities, or the project is stopped as a consequence of management decisions after the approval has been received.

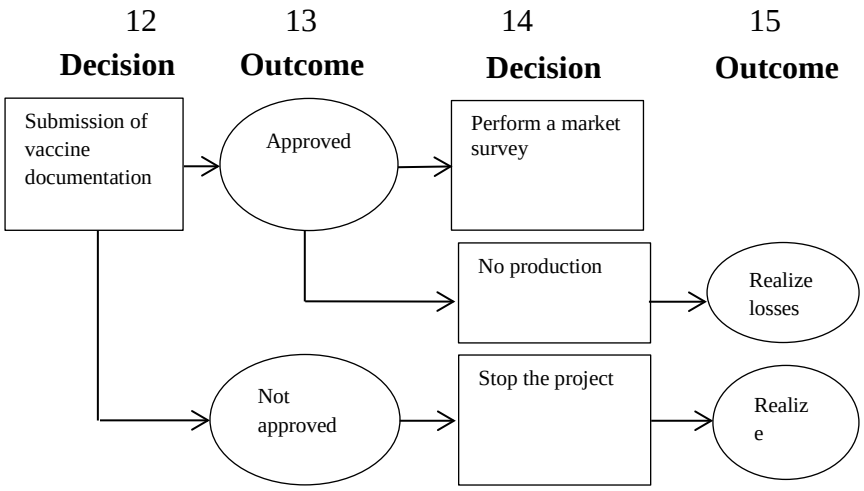


Figure 2.6: Documentation and approval phase

2.2.5. Decision tree for production and distribution

The assumed decision tree for the production and distribution phase is illustrated in Figure 2.7. Depending on the outcome of a market survey it is decided to launch the vaccine or stop the market introduction. The likely outcomes of the market survey are shown in the figure.

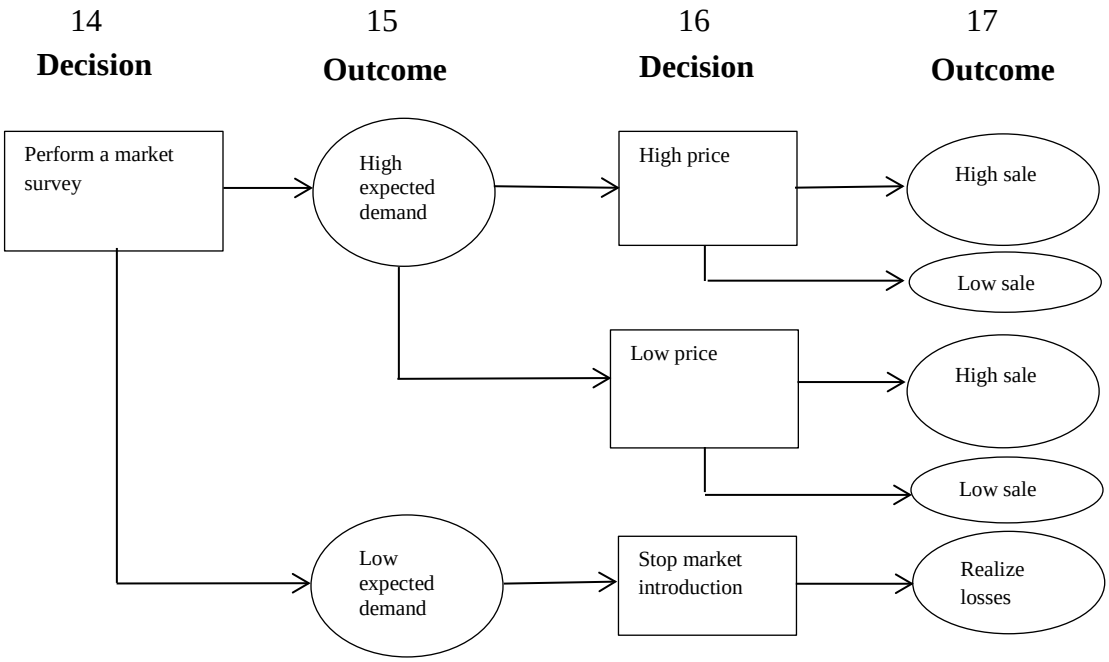


Figure 2.7: Decision tree for the production and distribution phase

If the decision "Perform a market survey" is chosen, then two alternative outcomes are assumed possible: "A high expected demand" or "A low expected demand". If the outcome "High expected demand" is observed, then there are two decision alternatives: "Charge a high price per vaccine dose" or "Charge a low price per vaccine dose". If the decision alternative "Charge a high price per vaccine dose" is chosen, then there are two possible outcomes: "A high expected sales income" or "A low expected sales income", and so forth.

If the decision alternative "Charge a low price per vaccine dose" is chosen, then the type of outcomes is the same as for the decision alternative "Charge a high price per vaccine dose", but the probabilities differ. If the outcome "Low expected demand" is observed, then only one decision is possible: "Stop the market introduction of the vaccine" with the outcome that an economic loss will most likely be realized.

If the decision option "No production" is chosen, an economic loss will also be realized.

3. Expected costs of a Campylobacter vaccine

This chapter attempts to quantify the costs associated with developing, producing and marketing a Campylobacter vaccine in the respective stages, and for the process as a whole. Furthermore, the chapter makes an assessment of the market potentials for such a vaccine.

3.1 Costs associated with the development

3.1.1. Research and Development (R&D) costs

Generally, data on research and development costs for specific drugs are difficult to get, primarily due to confidentiality concerns for competitive reasons. The present analysis is based on research and development costs in a Danish publicly financed research project with the overall aim to develop a cost-effective vaccination of poultry through three different vaccine candidates, (see Box 3.1).

In the CAMVAC research project, three candidate vaccines and delivery systems are investigated: 1) A Danish subunit vaccine; 2) A whole cell flagellar vaccine lead by a research group at Utrecht University in the Netherlands; and 3) Vaccination with the attenuated Salmonella strain lead by a research group from University of Arizona in the US.

The partners in the Danish subproject is the National Food Institute at the Technical University of Denmark (DTU-FOOD), Dianova, an independent SME unit owned by the Technical University of Denmark, that sell products and services covering e.g. laboratory analyses, vaccines, sera, consultancies and risk assessments. ACE BioSciences is a Danish biotech company that discovers and develops vaccines to fight serious infectious diseases. The last partner participating in the development of the Danish vaccine is the National Veterinary Institute at the Technical University of Denmark (DTU-VET).

The project is financed by the Danish Council for Strategic Research and is carried out during the period 2010 – 2014.

Box 3.1: The Danish CAMVAC project

Only the costs related to the Danish subunit vaccine are considered in the cost estimation. This vaccine candidate has not been assessed for use in chicken production before and thus four research tasks were planned to be included in the Danish subproject:

- Task 1: Establishing the optimal dose. The optimal dose of the protein vaccine is determined in a series of experiments on two-week old chickens in isolators
- Task 2: Challenge experiments in breeders. Ten breeder hens will be challenged in containment facilities with the homologous *Campylobacter* strain
- Task 3: Extended containment studies. In the case of significant impact on colonization, an extended challenge study against heterologous wild-type strains is conducted in containments

- Task 4: Field studies. In the case of success, field studies will be established in two conventional farms and one organic farm in Denmark. Furthermore, the vaccine will be evaluated in a farm in Indonesia under tropical conditions and low biosecurity measures.

The overall expenditure budget for the whole project was in 2009 budgeted to be 18.1 million DKK, corresponding to 2.4 million € (exchange rate 7.50 DKK per €). Of this sum, 147,195 € and 136,614 € were allocated to research groups at Utrecht University and University of Arizona, respectively, and 186,448 € were allocated to the development of a statistical decision tool and the assessment of economic and social prospects. By subtracting these expenditures from the total budget, it is crudely estimated that 1,948,623 € are allocated to biological and experimental R&D activities in the Danish subproject.

The costs divided into salaries, operating expenses and administration expenses are shown in Table 3.1. It shows that the expenses paid for salaries is about half of all budgeted expenses in the Danish project.

Table 3.1: Cost decomposition on salary, operating and administration expenses, €

	DTU-FOOD	DIANOVA	ACE Bioscience	DTU-VET	Total
Salaries	552,392	232,000	60,000	147,333	991,725
Operating expenses	232,133	130,000	42,667	98,667	503,467
Administration expenses	345,191			108,240	453,431
Total	1,129,716	362,000	102,667	354,240	1,948,623

Research and development costs of about 2 million € for discovering and investigating a new vaccine candidate might be considered as low. An important reason is that it is nearly impossible to estimate the "true" R&D costs, as new R&D activities typically are based on earlier R&D activities etc. This is also true with respect to the Danish vaccine as described in Box 3.2.

The biotech company ACE BioSciences in 2001-2005 worked with a promising protein Campylobacter candidate for human use. The protein vaccine type had some advantages compared to the live vaccine where large batches in the production process can fail. In 2006 both phase 1 and phase 2 showed very good results in the clinical tests. However, the pharmacy industry did not show any interest in the candidate at that time. The reason was that the industry simply did not believe in a potential market for the upcoming vaccine, so nobody was ready to buy the vaccine candidate from Ace BioSciences. Together with the Johns Hopkins University in Maryland and the U.S. Navy, Ace Biosciences carried out tests on soldiers from the U.S. Navy (Naval Medical Research Center, NMRC) in 2009 with financial support from the US Government. The vaccine trails failed and the trial results caused Ace BioSciences to sell everything including patents to TD Vaccines. TD Vaccines mainly worked on an E Coli vaccine. Later on the rest of work was handed over to Dianova and the maintenance of the patents was at that time still paid by TD Vaccines.

Box 3.2: History of the vaccine candidate

The experience illustrates the difficulties in determining the real R&D costs. However, from a decision making perspective past costs are "sunk costs" and should therefore be disregarded. Thus, in our model framework it is assumed that the management team has to decide whether to invest about 2 million EUR in the development in a new Campylobacter vaccine or if this real investment option should be abandoned.

3.1.2. Patent costs

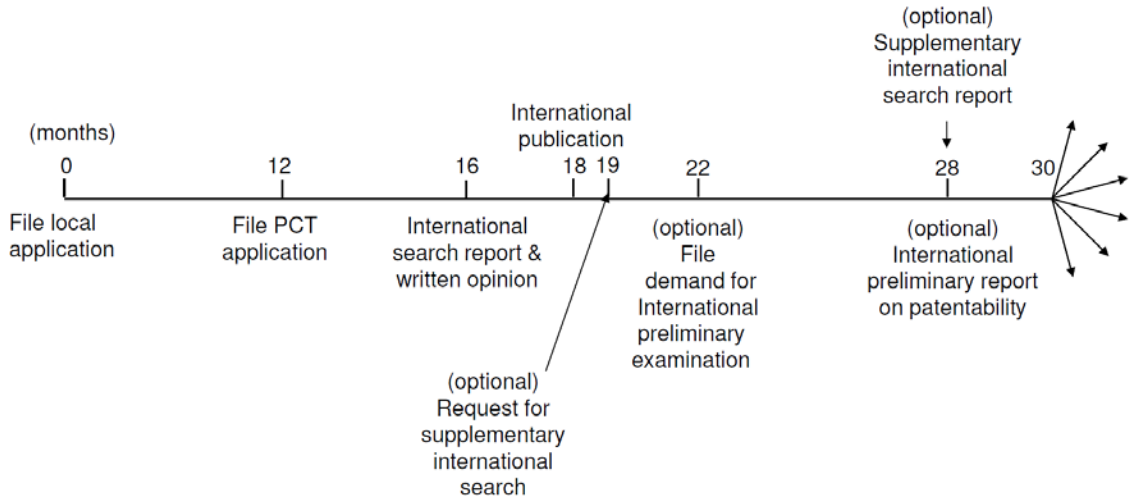
Because of market competition, it is crucial to protect intellectual property rights associated with new commercial research and development (R&D) activities. Consequently, the patent application and description is often made in the early stages of the R&D phase in order to secure the rights to promising test results or a broader described idea. A very detailed description of the patent application is not the scope of this chapter and the applicants' strategies determine the cost level and to some extent how the patent phase is carried out. But in general, the cost of a patent depends on the character and complexity of the invention. The broader and more complex the patent, optionally combined with a complicated third party patent portfolio, the more expensive are the procedures. However, the following stages are relevant to mention in order to illustrate the patent process and the associated expected costs.

An overall first step is to monitor news from the industry and to search patent databases (www.patbase.com) to identify competing and already existing patents in the area. This does however not guarantee that other patents do not exist. One possible problem is that it takes up to 2.5 years in the international system of Patent Cooperation Treaty (PCT) and one year in the traditional national system before the final patent application is handed in and is available in the database (WIPO, 2011). This "time lag" problem implies the possibility of other patents being given during the processes of applying. The main second step is to review existing related patents to analyze the competition from these patents. The third step is to write the application to the Directorate of Patents by using the

traditional national patent system in one country or to use the PCT system that consists of 144 states worldwide.

A time frame scenario is the following: local (Danish) priority application filing, a PCT filing (at +12 months), a PCT International Preliminary Examination (+ 19 months), a PCT National phase (+ 30 months), national applications, prosecution and grant (+40-50 months), European Patent (EP) national validation (Dianova, 2012). The first 30 months of the PCT system are illustrated in Figure 3.1 below. Typically, beginning with a national patent application in the home country of the applicant, and after 30 months the patent enters the national phase and the applicant expresses intention and takes steps to pursue to grant in various states (WIPO, 2011).

Figure 3.1: The PCT System



Source: WIPO (2011).

When it comes to application strategies, one strategy might be to use minimum explanation of the invention because competitors also read the patent description. In the beginning the description can be broader and later in the final patent application more narrow and specific. There exists many legal and interpretative aspects in the patent discipline and information and knowledge is truly a valuable part of the patent's product or idea. On the other hand, if the application is not clear enough from the beginning it might cause problems later on, because the formulation in the application limits the patent's usefulness and put some unintended constrains on the product.

A broad estimate on the cost of a patent application is about 67,000 € including different application fees and refunds. Additional costs are e.g. printing fees and other fees to maintain the patent in the entire patent's lifetime of 20 years according to the European Patent Organisation (2012) and the Patent Co-operation Treaty (2012). Many applicants tend to use professional assistance in their handling of application procedures etc., which add further costs to the patenting process. We assume that such

additional costs constitute 70,000 €, and hence that the total patenting costs amount to 137,000 €. The total time frame of the entire patent phase is assumed to be at least four to five years on a vaccine patent case without major problems during the different steps. The lifetime of the patent is 20 years if it is maintained (Dianova, 2012).

By nature, the patenting costs can vary considerably according to the decided type of patent and whether protection is national or covers the entire European Union (EU). In our case, we assume that the vaccine patent covers the EU for a period of 20 years. Due to the complexity of fees that have to be paid during the 20 years, such costs are not explicitly described in the model, but are assumed to be included in the additional costs to assistance, etc.

3.1.3. Testing and documentation costs

The testing procedure for veterinary vaccines is described by the World Organization for Animal Health (2012) and is summarized in Table 3.2 together with an estimate of the resource requirements for each component of the testing and documentation phase.

In order to obtain marketing authorization for a veterinary medicinal product, the applicant should be able to document the properties of the vaccine. Documentation requirements vary between countries. In the European Union, the documentation requirements are in principle similar to those for human vaccines with respect to safety attributes (whereas the requirements for documentation of effectiveness may be less strict for veterinary vaccines than for human ones). Official documentation requirements for the quality, efficacy and safety of veterinary vaccines are stated in articles 12 and 13 in EU Directive 2001/82/EC, as well as in various guideline manuals (EMA-1, EMA-2, EMA-3, EMA-4). Documentation requirements include:

- Qualitative and quantitative particulars of all the constituents of the product
- Description of the method of manufacture
- Therapeutic indications
- Dosage for various species of animals
- Explanations of precautionary and safety measures to be taken, if applicable
- Indication of withdrawal period
- Description of control testing methods employed by the manufacturer
- Results of physico-chemical, biological, microbiological, toxicological and pharmacological tests and clinical trials

In particular, the latter bullet is expected to imply costs, in terms of results of research and trials, which are closely related to the development and engineering phase as well as the testing phase. These trial costs are presumed to depend on the number of trials necessary to document the requested aspects which requires statistical power calculations. According to EMA-4, the appropriate sample size depends on the primary objective of the trial. For example, a trial sized on the basis of safety questions

may need a larger number of animals than one sized on the basis of efficacy or quality questions. Hence, the testing procedure involves a range of activities, spanning from laboratory testing, via controlled (clinical) testing in live animals to field testing of the vaccines.

Table 3.2: Elements in testing and documentation

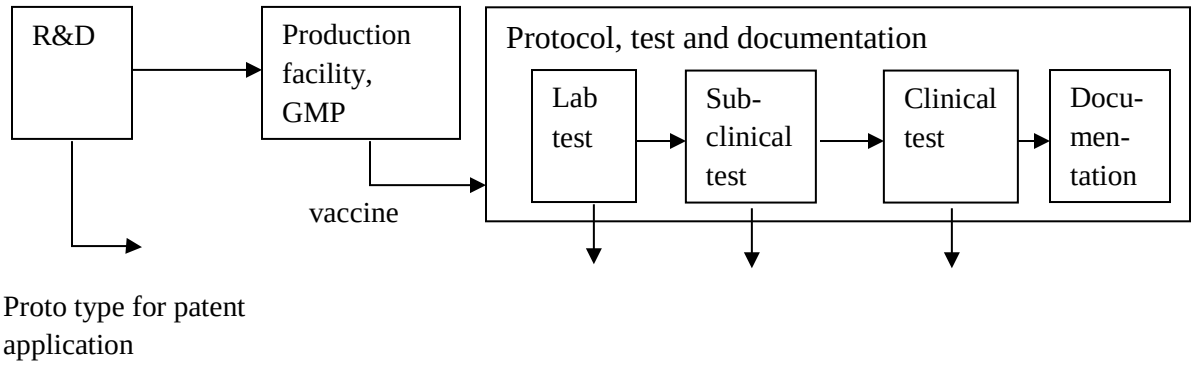
	Aim	Test procedure
Purity	Ensure freedom from extraneous bacteria, fungi, mycoplasma and viruses	Testing for a variety of contaminants. Tests can be performed on master seeds, primary cells, MSCs, ingredients of animal origin and on batches of final product prior to release
Safety	Intrinsic safety of the vaccine, of a single dose, of an overdose and of repeated single doses	Tests in relevant live animals. Testing requirements will depend on, whether the vaccine is a live vaccine or based on inactivated microorganisms
Virulence	Avoid transmission of organism to contact animals	Tests on groups of live animals
Environment	Risk to the environment, taking into account environmental risks for human health	May be done in conjunction with virulence testing
Efficacy/ potency	Efficacy tests of the final product vaccine	Under controlled conditions on sero-negative animals. Possibly supplemented with field efficacy studies
Interference	Avoid decrease in one productive immunological response caused by another component	
Consistency	Consistency in production	Test different batches for purity, safety and potency
Stability	Establish the validity of the expiry date	Potency test
Documentation	Collect and present test results, prepare application for approval	

Source: World Organization for Animal Health (2012).

In order to carry out the test phase, the development of a testing protocol is necessary. Furthermore, a test vaccine, resembling the expected final vaccine product to be marketed, needs to be produced and documented in accordance with Good Manufacturing Practice including guidelines for production, cleaning, etc. It is estimated that the development of a testing protocol involves three full-time expert months corresponding to a cost of 24.000 € and that the costs of producing about 21,000 doses of a test-vaccine amount to almost 40,000 €.

The testing procedure can be separated into three phases as illustrated in Figure 3.2: 1) Laboratory testing, 2) sub-clinical testing under controlled conditions and 3) clinical testing under real production conditions, where the vaccinated broilers are part of the production, which are sold for processing as broiler meat, i.e. the broilers in the experiment maintain their full market value.

Figure 3.2: Testing procedure



In the first testing phase (Lab test), it is assumed that the vaccine is tested on 100 broilers in a fully controlled laboratory setting; in the second test phase (Sub-clinical test), 1,000 broilers are assumed to be tested in an experimental production system; and in the third phase, the vaccine is tested on a flock of broilers (20,000 birds) in a real production setting on a commercial production plant.

The following provides a rough estimation of the costs due to trials forming the basis for the documentation of physico-chemical, biological, microbiological, toxicological and pharmacological tests and clinical trials. The estimation is done by budgetary calculations based on a number of technical and economic assumptions as outlined in Box 3.3. The calculation of the testing costs is summarized in Table 3.3.

Box 3.3: Test assumptions

Assumptions		
Interest rate	3%	
Wage rate – expert	49.07	€/hour
Wage rate- technician	38.13	€/hour
Effective working days/month	22.0	Days
Effective working hours/day	7.4	Hours
Price, baby chickens	0.13	€/broiler
Feed cost	0.93	€/broiler
Other unit cost	0.07	€/broiler
Total unit cost	**1.13**	**€/broiler**
Extraction and storage of samples	1.33	€/broiler

Table 3.3: Estimated costs of Campylobacter vaccine testing

	Investment	Investment horizon, years	Days	Cost, €
Development of test protocol				**23,966**
Expert hours			66	23,966
Production of vaccine for lab testing				
Expert hours			22	7,989
Technician hours			66	18,623
Capacity costs				20,000
No. of doses			21,100	
Raw materials			0,05	1,055
Total production cost of vaccine for testing				**39,678**
Cost of laboratory testing of Campylobacter vaccine				
Trial facility	150,000	1	50	21,164
Lab facility			30	19,984
Expert hours			44	15,977
Technician hours			110	31,038
Broilers				126
Sampling costs				133
Total lab trial cost				**88,422**
Cost of subclinical trial of Campylobacter vaccine				
Trial facility				
Lab facility			22	14,655
Expert hours			22	7,989
Technician hours			22	6,208
Broilers				1,130
Sampling costs				1,330
Total lab-field trial cost				**31,181**
Cost of clinical trial of Campylobacter vaccine				
Lab facility			22	14,655
Expert hours			22	7,989
Technician hours			22	6,208
Sampling costs				26,600
Total field trial cost				**55,451**

As mentioned, it is estimated that the development of a testing protocol costs 24,000 € and that the production of a vaccine for the testing process costs about 40,000 €. As these elements are essential prerequisites for initiating the entire testing procedure, they are included in the costs associated with the first testing phase which also involves direct laboratory testing work, amounting to 88,422 €, i.e. a total cost of the first testing phase of about 152,000 €. The costs of the sub-clinical trial phase are estimated

to be 31,000 € and the costs of clinical testing amount to 55,000 € according to the estimates in Table 3.3.

On top of the testing costs come costs of preparing the documentation. If we assume that the process of writing the documentation of the chemical, biological, toxicological etc. testing demands five expert months, and that the writing of description of manufacturing, precautionary and safety measures, withdrawal and control testing by the manufacturer requires another expert month, the total personnel requirement would amount to about 6 expert-months. With an assumed average Danish salary level of 8,000 € per month, the documentation cost amounts to about 50,000 € which should be added to the testing costs**.**

Supposing that the testing and documentation/approval phases lead straightly to the desired outcome – approval of the vaccine for the market along the "top path" of the two above decision tree diagrams – the costs of this phase amount to about 260,000 €.

If, however, parts of the testing phase only yield partly positive evidence, it may be decided to revise the testing procedure to pursue this evidence, which may require additional testing costs depending on the nature of the evidence. Similarly, if test results are satisfactory, but the documentation material fails to suffice for approval of the vaccine, revision of the documentation may take place, also influencing the cost calculation, with the probability of approval following the revisions assumed to depend positively on the efforts put into revising the documentation.

If it is decided to sell the tested vaccine after one of the testing phases, it is assumed that it can be sold at a value of 20 per cent of the expected net profit from the subsequent stages of the testing-manufacturing-distribution chain.

3.1.4. Production and marketing costs

Vaccine production and distribution includes different phases including starting material sourcing and control, production-seed and active-ingredient production, active-ingredient quality control, formulation and filling of finished product, final production quality control and release and packaging and shipment (IFAH, 2008). According to IFAH (2008) all these steps can be highly variable, depending on the vaccine in question and the number of dosses required. It takes on average 6-7 months to manufacture a new vaccine that has been developed in order to respond to an emerging pathogen or a new serotype.

Therefore, the costs of production – and marketing – of a new vaccine depend on a number of factors, including the life cycle of the product and capacity utilization in production, as well as several other factors.

The *product life cycle* as shown in Table 1.2 has three distinct phases: new product launch, market penetration and product maturity. Most price tiering has been seen with mature products. The challenge

for bringing new products to the market is to ensure effective management of the life cycle so that both manufacturers and the market will benefit (Batson, 1998).

Another critical factor in the economics of vaccine production is that of scale and *capacity utilization*. A pharmaceutical company will often have to take the decision to invest in production capacity at an early stage - in advance of knowing the real demand and before revenues are available to pay back investment costs.

In the past, capacity decisions were fairly straightforward as the manufacturers knew their domestic market segments and their likely export markets. The global market however, depends on excess capacity. Manufacturers can choose between two extremes: to focus only on the core market, which implies low availability, high cost, high price, and a risk of competition from manufacturers offering lower prices; or a global market focus with low cost and high revenues through market segmentation, but running the risk of threatening the domestic price structure through price tiering.

Good Manufacturing Practice (GMP) is now being introduced into vaccine production implying that investments in facilities, staff, and processes to maintain GMP compliance are driving production costs up. The ever-increasing “GMP spiral” demands more and more investment. Each step of the production process must be documented and validated. A number of pharmaceutical manufacturers now contract out parts of the process to contract manufacturers, particularly production scale-up, in order to lower the commercial costs.

Some literature (e.g. Milstein and Batson, 1998) suggest that for manufacturers the most profitable route is to maximize production volumes, serving all segments of the market at appropriate price points. However, unused capacity will have a cost. Capacity decisions are relatively immutable as the GMP requirements for biological products make capacity expansion both very expensive and time consuming. Thus, capacity investments imply higher prices because of high risks incurred by manufacturers.

Due to the many different factors, the costs of producing a new vaccine can therefore vary greatly for different types of vaccines and among different manufacturers. Furthermore, for competitive reasons the majority of drug manufacturers are not willing to disclosure their production and marketing costs. Thus, the production and marketing costs are rarely published and known to others than the company itself.

There are typically three types of costs involved in the production of vaccines. The first is the variable costs which is a unit cost that may include such items as vials. These variable costs are directly dependent on the production size. The next type of costs is the semi-fixed costs which are related to a fixed batch (which normally have a size of several thousand doses). If it is possible to produce a bigger batch size, then the cost per dose will decline. The last cost type is the fixed costs which are e.g. the investment costs for manufacturing and storage capacity. Within considerable ranges the fixed

production costs are typically independent of the number of doses produced implying that if the number of doses goes up, then the fixed costs per dose goes down. In general, the proportion of semi-fixed and fixed costs associated with vaccine production is much higher per dose than the unit variable costs.

The price of existing live vaccines for poultry on the Danish market is 0.01-0.02 € per dose. Market experts estimate that marketing and distribution costs amount to about one third of the market price of such vaccine and that such marketing efforts are necessary to obtain sufficient sales. This leaves two thirds of the market price for covering the production costs (including costs of covering the development of the vaccine). If we assume that full-scale production of the Campylobacter vaccine can be done at a cost similar to that of existing live vaccines, this is assumed to imply a production cost of 0.8 eurocent per dose and a distribution/marketing cost of 0.5 eurocent per dose.

These figures can be compared with estimates for the costs of production and marketing of drugs used in other modeling studies in the pharmaceutical industry. Kellogg and Charrnes (2000), for example, estimated the production costs to be 25 per cent of the revenue whereas the marketing expenses were assumed to be 100 per cent of the revenue the first year after launch of the drug and then decreasing to 20 per cent in the fifth years and the following years. In Borissiouk and Peli (2001) the direct costs (i.e. variable costs) are estimated to about 2.3 per cent of the revenue, whereas the marketing costs associated with the launch of the drug are estimated as 20 per cent of the peak sales and thus spread out three years around the launch year. Additional production and marketing costs in their study include e.g. construction of the sales force and other costs related to the launch of the drug. Compared to the 2.3 per cent variable cost share assumed in Borissiouk and Peli (2001), the variable costs were assumed to be 12 per cent in Trang and Takezawa (2002)'s case study of the valuation of a drug project in a Japanese subsidiary. This difference underscores the high variability in the production and marketing costs associated with the launch of new drugs reported in the literature.

3.2. Market potentials for a broiler vaccine

The market potential for a Campylobacter vaccine in broiler production is assumed to depend on the total broiler production, the current prevalence of Campylobacter in broiler flocks and the potential economic gains of primary producers of delivering Campylobacter free broilers to the processing stage. If the current flock prevalence of Campylobacter on a given market is relatively low, there will be a relatively lower demand for the vaccine in that market than if the prevalence were high. In general, farmers will be more prone to vaccinate if they can obtain a high economic reward of reducing their Campylobacter prevalence, however depending on the current profitability in broiler production, because vaccination requires financial liquidity.

3.2.1. Prevalence of Campylobacter

In order to evaluate the level and frequency of Campylobacter in EU, the European Food Safety Authority (EFSA) estimates each member country's prevalence of Campylobacter in poultry (EFSA,

2010). The report analyses 10,132 broiler batches sampled from 561 slaughterhouses in 26 European Union Member States, plus Norway and Switzerland, from 2008. The overall weighted mean prevalence of all 26 European Union Member States in the sample is estimated to 71.2 per cent. In general, there are large variations within each country but also between countries. The highest prevalence levels occur in Southern Europe with few exceptions and the lowest prevalence is registered in the Northern Europe.

Mean prevalence for each country is stated in Table 3.4 along with the total number of broilers slaughtered in 2008 and 2011. Greece did not carry out the Campylobacter survey, but according to Eurostat the 2011 Greek broiler production counts 113,647,000 slaughtered birds.

An estimate of the market potential for the Campylobacter vaccine in each EU member state can be obtained by multiplying the mean 2008-prevalence by the number of slaughtered broilers in 2011. This approach assumes that the market potential will be greater, the higher the current prevalence and the larger the broiler production.

Using this approach, we distinguish three different scenarios reflecting three alternative marketing strategies in terms of geographical orientation (Table 3.5). The first scenario covers all EU-27 member states where Greece is assumed to have the same (low) level of prevalence as Bulgaria (29.6 per cent), since Bulgaria is the closest neighboring country to Greece, with assumedly similar climatic and biological conditions. This scenario represents a potential market of 4,285 million doses per year. In the second scenario, we assume that the vaccine is primarily aiming at Northern European markets consisting of: Norway, Sweden, Finland, Denmark, Ireland, United Kingdom, Netherlands, Germany, Poland, Estonia, Latvia and Lithuania – these countries represent an estimated market potential of 1,827 million doses per year. The third scenario assumes that the vaccine is targeting markets with above EU-average Campylobacter prevalence (i.e. mean prevalence above 71.2 per cent) which targets a total market potential of 3,082 million doses or about 79 per cent of the entire poultry production in EU.

Table 3.4: Campylobacter prevalence and poultry production statistics

	%	Total poultry production (1000 birds)	
	Prevalence	**2008**	**2011***
Austria	47.8	63,000	67,835[6]
Belgium	31.0	242,231	304,487[7]
Bulgaria	29.6	35,748	52,266
Cyprus	30.6	11,131	13,639
Czech Republic	61.3	130,295	122,707
Denmark	19.0	101,967	106,074
Estonia	2.0	8,268	8,745[8]
Finland	3.9	55,233	57,446
France	76.1	706,342	1,030,212
Germany	48.9	438,467	705,052
Hungary	50.1	107,949	156,334
Ireland	83.1	65,399	65,399[9]
Italy	63.3	400,000	564,132
Latvia	41.0	13,906	14,641
Lithuania	41.5	8,228	41,884
Luxembourg	100.0	45	52
Malta	96.8	3,118	2,437
Netherlands	24.4	451,545	451,545
Poland	78.9	557,329	707,184
Portugal	82.0	173,069	197,216
Romania	77.0	160,743	182,488
Slovakia	73.6	52,996	49,813
Slovenia	78.2	34,086	31,843
Spain	88.0	594,734	703,727
Sweden	13.2	76,108	82,624
United Kingdom	75.3	816,216	930,423
Total EU (26 MSs)	**71.2**	**5,308,155**	**6,650,204**
Norway	3.2	62,235	
Switzerland	59.0	48,536	
Total (EU - 26 MSs and two non-MSs)		**5,418,925**	

[6] 2008 data from Eurostat
[7] 2008 data from Eurostat
[8] 2009 data from Eurostat
[9] 2008 data from EFSA
Note: For Lithuania the two sources EFSA and Eurostat differs significantly, suggesting some uncertainty with the data for Lithuania.
Source: EFSA 2010 and Eurostat* data

Table 3.5: Three different scenarios of market potential

		Number of countries	Total production in 2011 (millions)	Estimated market potential (millions of doses)
Scenario 1	EU-27 (incl. Greece)	27	6,764	4,285
Scenario 2	Northern countries of Europe (incl. Norway)	12	3,233	1,827
Scenario 3	Countries with prevalence larger than mean (71,2%) of EU (incl. Norway and Switzerland)	11	3,901	3,082

3.2.2. Economic margins in European broiler production

In addition to Campylobacter prevalence, profitability in broiler production is also considered to be an important determinant for producers' demand for a Campylobacter vaccine because producers with low profitability in production are presumed to be more reluctant to take on an additional cost with risky or uncertain economic returns such as a vaccination of broilers against Campylobacter.

Economic margins in poultry production in different EU member states are illustrated in Table 3.6 where data from individual specialized and non-specialized poultry farms from European Farm Accountancy data (FADN) are weighted to a "country margin" of the production of poultry named Gross Margin I (GM I ~ output value, net of animal-specific unit costs such as feed and other raw materials) and Gross Margin II (GM II ~ GM I, net of quasi-fixed farming overhead costs such as labour and machinery). The farmers in each country are assumed to get the same price per kg of live weight calculated from a one to three years period of time provided by the Eurostat agricultural price statistics.

According to the FADN data covering the years 2006-2008, seven of the countries (Poland, Belgium, Germany, United Kingdom, France, Italy and Spain) had a gross margin (GM II) larger than 0.25 € per broiler (Table 3.6) suggesting that broiler producers in these countries might have the financial capacity to undertake Campylobacter vaccinations representing a total market potential for vaccine in the area of 3,458 million doses per year.

Table 3.6: Economic margins in broiler production in selected EU member states (€ per broiler)

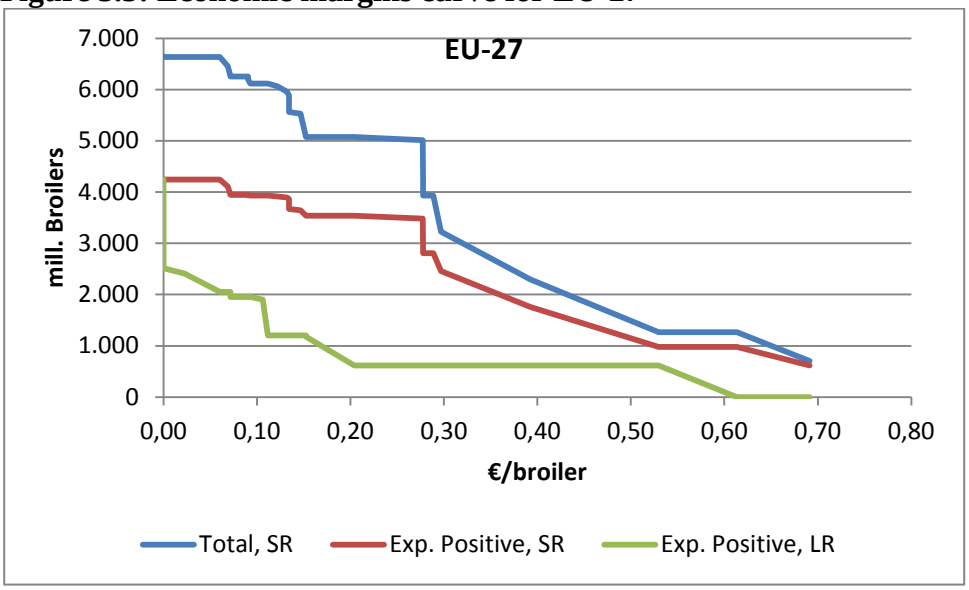
		GM I	GM II
Austria	2006-2008	0.68	0.13
Belgium	2006-2008	0.46	0.28
Bulgaria	2007-2008	0.41	0.11
Denmark	2006-2008	0.34	0.12
France	2006-2008	1.45	0.39
Germany	2006-2008	0.91	0.29
Greece	2006-2008	-0.19	-0.69
Hungary	2006-2008	0.42	0.13
Ireland	2006-2007	0.29	0.20
Italy	2006-2007	1.10	0.61
Netherlands	2006-2008	0.35	0.15
Poland	2008	0.40	0.28
Portugal	2006-2008	0.24	0.07
Romania	2007-2008	0.44	0.06
Spain	2006-2008	0.94	0.69
Sweden	2006-2008	0.52	0.09
United Kingdom	2006-2008	0.49	0.30

Source: Own calculations of European Farm Accountancy data (FADN) and Eurostat agricultural price statistics.

3.2.3. Demand curve patterns for the developed vaccine

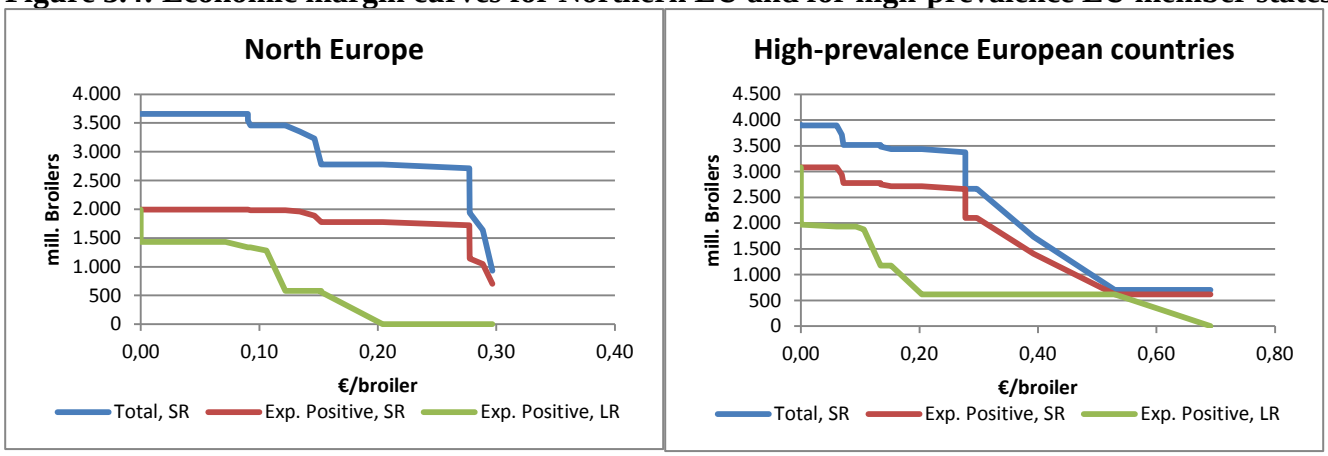
Shapes of demand curves for Campylobacter vaccine may be derived by combining economic margin figures and production quantities in the three scenarios. Curves for gross margin II and net margin have been drawn in Figure 3.3. Two GM II-curves have been drawn; one curve representing total broiler production and another curve representing total expectedly Campylobacter-positive broiler production with a GMI per broiler above a certain level. Whereas the first might indicate the maximum potential size of the market, if a mandatory vaccination program were assumed or if there is no information available about Campylobacter status at the time of taking the vaccination decision, the second indicates the maximum potential size of the market, if the vaccination decision can build on fairly precise information about expected Campylobacter status. As a number of risk factors for Campylobacter prevalence have been identified (Sommer & Heuer, 2007; Sommer & Rosenquist, 2011), such as seasonality, quality of broiler production facilities, etc. which might assist in determining the expected Campylobacter status, the latter is considered to be more realistic in a voluntary setting.

Figure 3.3: Economic margins curve for EU-27



The pattern of these curves may be assumed to reflect the pattern of demand curves for a Campylobacter vaccine if we rely on the assumption that the GM II-figures reflect the economic capacity of farmers to buy vaccines. As fixed capacity costs are not subtracted in the calculation of GM II, this figure could be interpreted as a maximum willingness to pay for vaccine in the short run (SR), whereas the willingness to pay is expected to be lower in the long run (LR) (but might still be presumed to exhibit a pattern similar to that shown in the demand diagrams). Based on the FADN data from a range of EU member states for 2006-2008, net margins per broiler were also estimated to represent the long-run ability to pay for vaccination. Assuming that the pattern of the long-run curve is reflected in the demand curve for the Campylobacter vaccine, a price elasticity of -0.69 was estimated for the EU-27 market using log-log regression.

Figure 3.4: Economic margin curves for Northern EU and for high-prevalence EU member states



Similarly, Figure 3.4 displays the pattern of GM II- and net-margin curves for the two other market scenarios: the North European market scenario and the High-prevalence member states scenario. Assuming again that the pattern of the net-margin curves reflects the pattern of the demand curve for Campylobacter vaccine, the price elasticity for the vaccine was estimated to -1.56 in the North Europe scenario and -1.11 in the High-prevalence scenario.

The position of the respective vaccine demand curves is calibrated on the assumption that broiler producers face a price reduction if they deliver Campylobacter-positive birds. Inspired by a Danish example, it seems realistic to assume a price reduction of 1.5 eurocents per broiler if the flock is positive.

3.3. Expected net present value of the developed vaccine

Provided that all phases in the development and testing procedure are successful, the above data and assumptions are combined into a whole-chain calculation of the costs of development and production of a Campylobacter vaccine as well as the potential profitability in such a project. The calculation is shown in Table 3.7, expressed as Net Present Value (NPV) in thousands € (in 2010 price level) assuming that the vaccine is marketed in all EU-27 member states.

Table 3.7: Direct costs, NPV (1000 €, 2010 price level)

Thousand doses	315,539
Sales revenue	44,064
R&D	1,949
Patent	125
Test & documentation	184
Production	19,252
Distribution cost	11,750
Total costs	33,261
Net Present Value	10,803

The scenario suggests that 315 million doses of vaccine could be sold every year which adds up to 3.2 billion doses over a 10-year production horizon. Assuming an expected sales price of 2 eurocents per dose in 2017-2027 (a high-price sales strategy), the net present value of these sales is calculated to 44 million €, taking into account an assumed development period of 7 years and a production horizon of 10 years, and the NPV of gross margins from these sales is 14.7 million €. If instead a low-price sales strategy is chosen, expected sales volume would be higher (3.9 billion doses over 10 years - because of the price elasticity of -0.69), but the margin on each dose will be lower. This would imply a present value of gross value added of 3 million €. Hence, in the present calculation, a high-price sales strategy can be considered as the dominating strategy.

In the present calculation, development costs amount to 5-6 per cent of the total costs whereas production costs constitute almost 60 per cent and distribution costs the remaining about 35 per cent.

This is somewhat in contrast to the structure in other vaccine-related cost calculations in the literature (e.g. World Bank and GAVI Alliance, 2010), where fixed costs (including development costs) are found to constitute a significant majority of the costs. However, as the requirements for clinical testing, documentation etc. are much stronger than for veterinary vaccines, it is expected that development costs should constitute a smaller share in this case than for human vaccines.

The above decision tree framework enables economic calculations of Campylobacter vaccine production from different perspectives, including a "direct" and a "probabilistic" perspective. Results from such calculations are presented in Table 3.8.

Table 3.8: Expected profits (NPV)

	Strategy/perspective	
1,000 €	Direct	Probabilistic
R&D	10,803	-1,938
Patent	12,752	89
Test & documentation	12,877	391
Production and distribution	13,062	8,655

The table evaluates the NPV of going one step further in the development process assuming that the current stage has been reached successfully and treating costs from previous stages as “sunk costs”.

For example, in the "direct" strategy/perspective, we calculate the NPV under the assumption that the project will carry through from the current stage and to the final production and distribution stage and that all phases of the stochastic process yield the desired outcomes. Under this assumption, the calculated net present value of the project, as evaluated prior to the R&D stage, is 10.8 million €. The NPV increases as we proceed along the process because the (sunk) costs of the intermediate stages have been laid behind. This perspective could be considered as an "optimistic" perspective.

In the "probabilistic" strategy/perspective, we calculate the NPV at different stages in the development process under the assumption that the project has been successful so far (i.e. failures in previous stages are treated as sunk costs), but that there is risk related to decisions and outcomes in the subsequent stages. For example, at the testing stage, we assume that R&D and patenting stages have been completed successfully, but that outcomes of testing and/or documentation are stochastic, and furthermore that decisions to be taken in subsequent stages are random (with equal probabilities of each decision option in the respective decision stages). Thus, increases in NPV from one stage to the next represent the sum of costs that have been laid behind and removal of risk elements. This perspective could be considered as a "pessimistic" perspective. From this perspective, the expected value becomes positive only after successful completion of the patenting phase.

The size of the market for the developed Campylobacter vaccine also constitutes an uncertainty to the economic assessment of such a development project. As mentioned previously, we consider three

alternative market scenarios: a scenario, where the entire broiler sector in EU-27 is the relevant market ("EU-27"), a scenario, where Northern EU is the market ("North Europe"), and finally a scenario, where countries with high Campylobacter flock prevalence is the target ("High Prevalence member states"). The importance of these scenarios is illustrated in Table 3.9.

Table 3.9: NPV's in alternative market scenarios (1000 €)

	EU-27	North Europe	High Prevalence member states
Thousand doses	315,539	68,304	211,948
Sales revenue	44,064	9,539	29,598
R&D	1,949	1,949	1,949
Patent	125	125	125
Test & documentation	184	184	184
Production	19,252	5,442	13,465
Distribution cost	11,750	2,544	7,893
Total costs	33,261	10,244	23,617
Gross Present value	13,062	1,553	8,240
Net Present Value	10,803	-705	5,981

Whereas the "EU-27" scenario naturally represents the largest market, the "High Prevalence member states" scenario appears also to represent a relatively large market and hence may reflect a relatively high profitability (and hence a higher economic ability to vaccinate) in broiler production in some of the member states with high Campylobacter prevalence, implying that these countries are also dominating the demand in the "EU-27" scenario. Demand for the vaccine in the "North Europe" scenario is lower than in the two other scenarios. In general, the unit costs of the vaccine are not dramatically different between the three scenarios, although higher in the “North Europe” scenario.

4. Real Option Valuation

4.1. Introduction

The commercial success of new vaccines is highly dependent on research and development (R&D) activities which are complex, dynamic and uncertain. Therefore, it is an important managerial decision to dynamically allocate resources to the best scientifically and financially founded projects. Three main features are typically associated with R&D activities:

- Irreversibility of investment expenditures
- Uncertainty about the future cash flows of the project
- Timing of the project investments

Thus, when it is decided to invest in the development of a new pharmaceutical product, it is not known if a new marketable product will come out at the end of the project. High uncertainty is associated with the future cash flow; and this is especially true for investments in new vaccines and drugs. In R&D, risks and returns are typically highly correlated. The higher the risks, the higher are also the potential returns on investments.

The opportunities and risks of R&D investments may be valued through real options valuations. Real options are generated through R&D activities, which may create the option to sell a new "real" product or service to the market sometime in the future. Many research and development (R&D) strategies may be enhanced over time if they prove to be successful in ways that only become apparent as time goes by. Furthermore, many investments can be made in stages, retaining flexibility in order to respond to future, yet unknown, conditions. In addition to the technological risks, the product developments in the pharmaceutical industry are also exposed to a significant amount of economic uncertainty, which is a function of both endogenous factors (e.g. internal transfer pricing, costs) and factors exogenous to the project such as market prices and interest rates.

In an uncertain and dynamic world it should be acknowledged that R&D investments and other strategic decisions are not merely a cost but rather an option creation. By spending now a relative small amount of money it might be possible to acquire the later "right" to undertake one or more follow-up investments with a much more profitable cash flow than the initial project. To understand the implications of these "strategic positioning investments", decision-makers involved in R&D projects should adopt a much broader view of potential markets, envisaging segments and product lines beyond those in which it is currently active (Borissiouk & Peli, 2001). Real options theory may help to explain, how many firms in the biotechnology industry have significant valuation despite having no product revenue because their products are in early stages of development. In the past ten to fifteen years investors have bid up the stock prices showing promise of developing a new profitable drug.

Although real option analysis has been recommended as an emerging valuation method for high-risk investment projects, former surveys have drawn an ambivalent picture of real option usage in general. Hartmann & Hassan (2006) provide an in-depth analysis of collected empirical data regarding the application of this new tool in the pharmaceutical sector by presenting the internal view from the pharmaceutical companies themselves and the external view from the health care departments of financial service firms. Real options in R&D stages, reasons for reluctance in the employment of real options and their assumed future prospects are elucidated. Vollrath (2001) surveyed the capital budgeting approaches of the largest German companies and some others from real option branches including pharma. Real options ranked at the lowest position. The knowledge of the real options approach constitutes 30 – 35 per cent depending on the company level in question. The abandonment was explained by the complexity of the approach that resulted in a black box problem (cited from Hartmann & Hassan, 2001).

According to Hartmann & Hassan (2001) risk analysis is mainly provided by decision trees (DT), scenario and sensitivity analysis, although Monte Carlo simulation and payback period also have some dissemination. The far most important obstacles for the usage of real option analysis by pharmaceutical companies are the assumed complexity of the real options approach and the lack of acceptance from decision-makers and customers (Hartmann & Hassan, 2001).

Regarding the different real option pricing techniques, it is obvious that a standardisation has not taken place in pharmaceutical R&D so far due to the fact that - in some cases – different case studies present different approaches. However, there seems to be a tendency in academia and the consultancy sector towards the binomial lattices (e.g. Copeland and Tufano, 2004) that combine the abandonment of complex mathematics and the possibility to include the technical risk of a project provided by its success rate (Hartmann & Hassan, 2001).

4.2. Shortcomings of traditional economic valuation methods

As argued above, R&D projects in the pharmaceutical industry, as well as in many other industries, often require staged investments to develop new products that may be commercialized. Thus, whether additional investments will be committed in specific stages of the development process depend on the outcomes of the previous R&D phases, the newest information concerning the expected demand of the products in different markets, capital funds available for investment in the R&D portfolio and many other factors that may have impact on the managerial discretion.

However, at pointed out by e.g. Dixit & Pindyck (1994) and Triantis (2003) the use of traditional discounted cash flow (DCF) or net present value (NPV) analyses does not properly capture the value of investments whose cash flows are conditional on future outcomes and managerial actions, and which thus have complex risk profiles. Cash flows are often estimated without explicitly recognizing how they depend on future investment or operational decisions. Furthermore, a single risk-adjusted discount

rate is often employed. The discount rate is typically the company's weighted average of capital (WACC), which however may disregard changes in the risk of a R&D project over time.

According to Triantis (2003) two advantages of looking at investment opportunities as real options have emerged. First, insight has been generated that provides new perspectives for the evaluation of investment opportunities. For example, the fact that an option may become more valuable if the volatility of the underlying assets increases. Second, analytic techniques have been developed that provide better evaluation of investments with embedded opportunities than do the standard DCF and NPV approaches.

4.2.1. Investment decisions in biotechnology firms

The basic idea of investment theory is to determine how much an investor should pay today in order to receive the right to a certain cash flow in the future. Some overall principles are guiding how future sequences of cash flows should be transformed into a "present value". The first principle is that a euro earned today is worth more than a euro earned some time in the future. Thus, there is normally a positive expected return associated with investing some money and this return should also cover the impact of inflation on the purchasing power on the invested money. Second, investors prefer typically a euro for certain instead of a euro on average. Therefore, the discount depends on the level of risk as well as the investor's risk aversion. Third, if the net present value (NPV) of the cash flow is positive the usual recommendation is to accept the project, and to make a rejection if the NPV is negative.

If all cash flows and the cost of financing are known with certainty, methods such as NPV and DCF are not controversial to use. However, when the cash flows and/or the financing are uncertain, no agreement has been reached about the correct methods to adapt. Although maybe theoretically sound, there are at least two critical problems associated with the use of these standard approaches in circumstances characterized by uncertainty. First, the expected cash flows typically do not reflect the flexibility that exists in the investment and the assets producing these cash flows. Second, the cash flow at different points in time may require different discount rates to appropriately reflect their risk. Thus, using a constant discount rate may lead to significant errors in the valuation of the cash flows (Triantis, 2003).

Managerial flexibility creates real options. Flexibility is valuable if volatility is present or, in other words, if contingencies arise to which one needs to react. Examples of volatility are technical risks (side effects or production problems) and market risks (market shrinkage, rejection of a drug by consumers, or an economic downturn) (Loch & Bode-Greuel, 2001). Continued corrective actions based on new information are at the heart of successful R&D management, and central to strategy making in general.

R&D risks may have both negative and positive effects on the performance of an R&D project. A methodology has been proposed in Wang & Yang (2012) to analyse R&D risks and organize R&D flexibility based on real option analysis. Their suggested methodology first identifies the potential

risks, then recognizes possible R&D options to resolve the risks and then applies a real option valuation method, as developed by Huchzermeier and Loch (2001), to evaluate and choose the options that maximize the value of the R&D project. Thus, the intention is to help R&D managers improve their managerial flexibility to capture opportunities and avoid treats.

Another important issue in capital budgeting in biotechnological companies is the decision problems associated with limited resources. In many, if not most, pharmaceutical companies there is not one, but a whole portfolio of new drug R&D projects. As noted by Borissiouk & Pell (2001), these companies do not always have sufficient research and development (R&D) resources, such as financial resources, people and facilities etc. to carry out all value added projects at the same time. Therefore, R&D projects often compete for the same scarce resources, implying that the amount and timing of resource allocation are of great importance in capital budgeting. The available resources depend on how many R&D projects that are stopped during the research and development phases due to technological failures (e.g. disappointing clinical tests results) or due to unfavourable market prospects (e.g. projections of low demands for the medical product). Resources released from abandoned projects may be reallocated to other R&D projects, which may then be completed sooner than originally planned. However, this shifting in resource allocation among projects is hampered by the stochastic nature of successful and unsuccessful results in the on-going projects. An example of a stochastic optimization model for selection of an optimal drug product portfolio using real options valuation techniques is presented in Rogers et al. (2002).

Thus, the traditional capital budgeting methods are incapable of allocating R&D resources to the best projects, as they do not account for managers' ability to decide proactively to any changes in future uncertainty. They do not consider the value of the option to wait and see and revise the initial strategy if future events are different from what was originally expected or to utilize follow-on opportunities if initiated projects perform better than initially expected (Borissiouk & Pell, 2001).

4.2.2. Limitations of decision tree models for investment evaluation

Compared to a traditional NPV calculation where neither cash inflows nor cash outflows are probability adjusted, a simple decision tree model as shown in Figure 2.2 is better to account for uncertainty.

Using such a simplified decision tree approach, it is possible to estimate the expected net present value (ENPV) which includes all costs and revenues from the research project, weighted by their compound probability of occurrence and discounted back to the present. Many companies apply the expected present value (ENPV) technique for its investment decision by adopting some type of decision tree models. It adjusts the value of R&D projects for their technological risk (presented by probabilities of success in the drug development process), but ignores their economic risk and related value of managerial flexibility.

The (ENPV) method takes into account the fact that costs and revenues in later phases are only incurred if the earlier phases are successful. In effect, this amounts to including abandonment options, or the flexibility of stopping a project if a phase is not successful, which is common practice in the pharmaceutical industry. Thus, this ENPV is not the "naïve straw man" sometimes considered in the financial literature as a contrast to options analysis (the straw-man approach would include all costs with certainty, as if the project was pursued even after a testing phase had failed) (Loch & Bode-Greuel, 2001).

Compared with a simple DCF analysis which is not using a decision tree approach and which may result in a negative NPV, the decision tree valuation may be significantly higher, because it recognizes the flexibility to choose at each decision point (in the event of a failure in the respective phase) the one of the remaining options that has the highest NPV.

Although a simplified decision tree approach as shown in Figure 2.2 to calculating the expected net present value (ENPV) is an improvement compared to traditional NPV analysis, it still has a number of weaknesses. The first weakness is that the decision model – as already noticed - only takes account of the technological uncertainty but not of the economic uncertainty. By disregarding the economic uncertainty, the economic value of the project may be underestimated because the flexibility to change the vaccine development process according to the resolution of the economic uncertainty is not accounted for. Second, the decision tree model uses a constant discount rate, which represents the project's cost of capital. However, by using a constant discount rate, the dynamic changes of the risk of the project resulting from both changes in environmental factors as well as managerial responses are ignored. The consequences of this ignorance are further elaborated in the following section.

4.2.3. The estimation of capital costs in discounting

When cash flows have been projected they should be discounted back to their present values. The rate of return on comparable projects should be used as the discount rate as they represent the opportunity cost of capital invested in the project. Identifying investments with comparable risks may however be challenging. The risk of a project depends not only on the volatility of underlying variables such as input and output prices, but also on other key variables such as degree of operating leverage, the timing of future investments in the project and the extent to which management can control the future cash flows. Even small differences in these project characteristics can translate into significant differences in project risks, and thus the discount rate that should be used for valuation (Triantis, 2003).

In investment evaluations, the weighted average cost of capital (WACC) is often applied. The assumption made is that the firm as well as the new project share the same risks. This assumption may be valid for some projects that have the same risks at the whole company, but it is typically not a valid assumption for totally new R&D projects that intend to innovate completely new products or items. High risks of failures as well as opportunities for unexpected rewards are embedded in the development

process. Therefore, choosing an appropriate discounting rate should be closely tailored to analysing the profile of the project.

A common argument is that riskier cash flows should be discounted at higher discount rates than less risky cash flows. This method is widely applied in investment appraisals. However, this method has been criticized as it implicitly assumes that uncertainty is always something negative which should be avoided. As argued previously uncertainty might however also provide flexibility in decision making which has a value on its own. The flexibility makes it possible to take advantages of future opportunities and at the same time makes it possible to avoid future losses. For these reasons, it seems to be incorrect just to discount projects with higher risks with a higher discount rate.

As an alternative, it has been suggested to account for risk in capital budgeting by finding the certainty equivalent value of each cash flow and then discounting these with the risk-free interest rate. This method is not without problems as it is difficult to estimate the certainty equivalents of the cash flows as well as the risk-free interest rate.

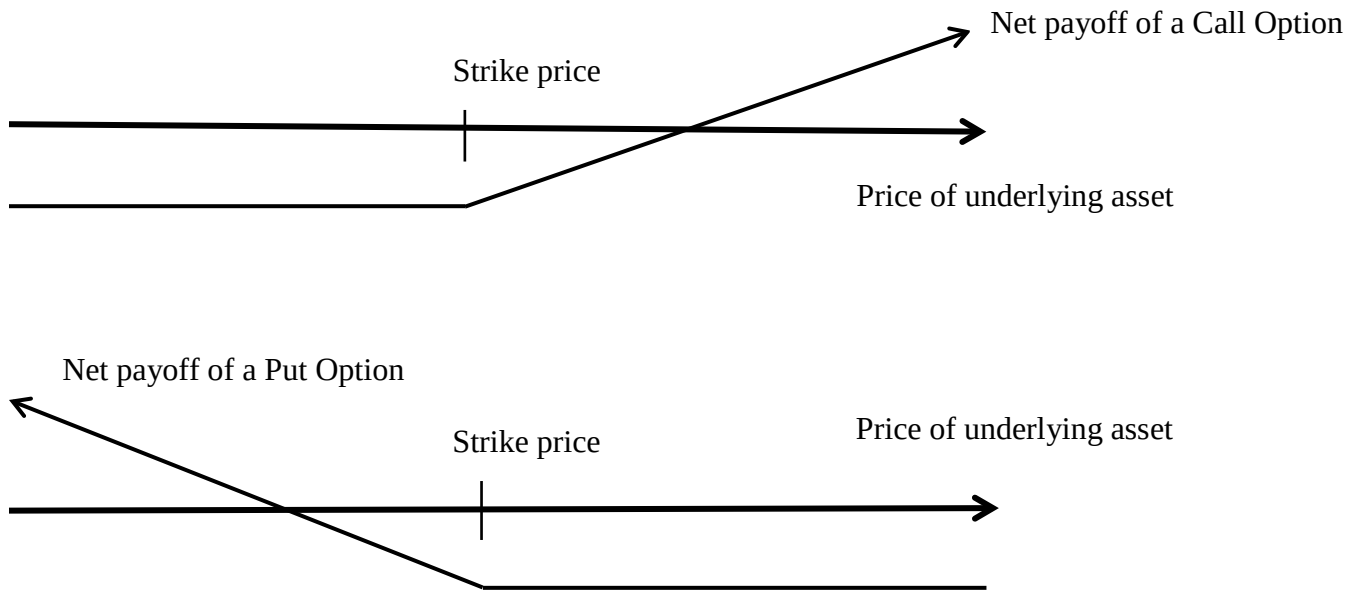
4.3. Real options in the development of new vaccines

4.3.1. Characteristics of real options

Recently, the concepts of options theory have been extended from the financial markets to investments and strategic decisions relating to physical assets in an uncertain environment – called real options (Yeo & Qiu, 2003). An option gives a right but not an obligation to buy or sell a share of stock at a specific price (called the exercise price or strike price). Thus, the payoff of an option can never be less than zero, independent of the underlying asset. From this it follows that the value of an option can never be negative, (Smit & Trigeorgis, 2004). The seller of the option has the obligation to deliver the asset if the option is exercised. In return she receives the exercise price.

Financial options are options related to financial assets. A “call” option gives the right to buy a stock, and a “put” option gives the right to sell a stock. If the option can be exercised before maturity, it is called an American option and if only at maturity it is called a European option. The payoff diagrams for a call option and put option, respectively, are shown in Figure 4.1.

Figure 4.1: Payoff diagrams for a Call Option and a Put Option



For a call option (i.e. the upper part of Figure 4.1) the net payoff is negative (and equal to the paid price for the option), as long as the value of the underlying asset is less than the strike price. When the price of the underlying asset exceeds the strike price, the gross payoff is equal to the difference between the value of the underlying asset and the strike price. The net payoff is then the difference between the gross payoff and the price of the call option. For a put option (i.e. the lower part of Figure 4.1) it is just opposite: if the price of the underlying asset is higher than the strike price, then the option will not be exercised and will be worthless at maturity. However, if the value of the underlying asset is less than the exercise price, the gross payoff will – as in case of a call option – be equal to the difference between the strike price and the value of the underlying asset; and the net payoff will as before be the difference between the gross payoff and the price of the put option. The call option is particularly relevant to evaluation of investment projects.

The real options concept is based on the model for financial options developed by Fischer Black and Myron Scholes in 1973, (Black & Scholes, 1973), which is an approach for calculating the value of financial options, i.e. rights to buy or sell financial instruments such as stocks, bonds and commodities at a specified price (the strike price) before a specified date (the expiration date). The concept of real options is using the same principles as financial options to value investment opportunities, however not in financial markets but in real markets for products, technologies or services. Therefore, real options can be seen as opportunities to invest in, or liquidate, a business' opportunity to sell new products or services in the future as a result of a successful innovation and development process. They result from the company's ability to change and optimize R&D activities over time as new information becomes

available or as uncertainties are resolved; and they are exercised through the strategic choices made by the company.

However, executives have pointed out that options embedded in management decisions are must more complex and ambiguous than financial options. These executives are concerned that it would be dangerous to try to reduce those complexities into simple option models such as the Black-Scholes model, which only include rather few variables (Copeland & Tufano, 2004).

Copeland and Tufano (2004) describe a number of differences between financial and real options, Firstly, the information needed to value and make decisions about financial options is typically much more accessible than for real options. For example, stock prices are available on the stock market whereas the value of a new drug cannot be observed in any meaningful way, but may be guessed, subjectively estimated or based on past performance of similar drugs. Secondly, the clarity of the options' terms is usually much clearer for financial options than for real options. No unambiguity is really involved in the right to exercise financial options whereas for real options it is often unclear what the owner of a real option has the right to buy and/or how long that right will exist. Even in the case that the underlying asset is rather well defined – e.g. construction of a new plant – the maturity of this option may be undetermined. Often the owner of a real option has no exclusive rights: You may have the option to build a new plant, but the same right may others also have (Copeland & Tufano, 2004).

Good management is as much about making decisions at the right time as making the right decisions. Therefore, Copeland and Tufano (2004) argue that the biggest problem with real option methods is not technical but managerial because of a disconnection between the way that managers value options and the way the manage them. According to these authors, there is overwhelming evidence that financial options are exercised suboptimally and therefore it cannot be expected that holders of far more complicated real options behave in a more rational manner.

4.3.2. Classification of real options

There exist different types of real options, and this section provides an overview of the basic types of options found in the literature that may be embedded in real investments. Special emphasis is put on real options that are of relevance to R&D projects in the pharmaceutical industry. According to Smit and Trigeorgis (2004) real options may be summarized into the following main types: Options to defer; Growth options; Options to abandon; Options to expand or contract; Options to temporarily shut down; and Options to switch (e.g. inputs or outputs). In the following, Options to temporarily shut down are disregarded, as it is believed that this type of option is of minor relevance in pharmaceutical R&D activities, where the highest share of the total costs is incurred in the construction of production and marketing facilities.

Box 4.1: Classes of options

Deferment Options

Opportunities to defer some decisions are probably the most well-known and most researched type of real option (e.g. Dixit & Pindyck, 1993). A decision or even a project that can be postponed might allow for more learning and experimentation about the potential outcome. The option to defer is especially valuable if there is high economic uncertainty about the future cash flows of the project, if the project possesses a long investment horizon (e.g. because of patent rights), or if the investment expenditures are irreversible. But when the entrance of new competitors is highly possible, then options to defer may have minor influence on the investment decisions. The option to defer may be worthless in the case of biotechnological projects (Borissiouk & Peli, 2001)

Growth Options

Real growth options provide often the possibility of investing in the follow-on opportunity of the initial project if the latter works out well, and may include e.g. the opportunities to explore new products and/or markets. Growth options are often compound options that are options on other options. In the real options theory, applications of compound growth options are commonly found in a number of industrial projects, but are especially relevant for pharmaceuticals where R&D projects create the options to make further research or testing or to commercialize the obtained results.

Abandonment Options

Abandonment, exit or disinvestment options enables the investor to exit when opportunities do not develop as expected, and hence minimize losses and divert project resources to other uses. A biotechnology project might be abandoned if R&D results are disappointing, testing indicates no or insignificant biological effects or market conditions are declining severely. The exercise of the option to abandon is equivalent to the exercise of the financial American put option (Borissiouk & Peli, 2001).

Options to expand or contract

During the life of a project, it may possible to alter the scale of the project by expansion or contraction of the project scale.

Switching Options

Switching or sourcing options make it possible to develop multiple input sources for content, channels and platform. Alternative outsourcing arrangements are examples from the manufacturing industry. Project development packages can be subcontracted out to third parties as is well-known in the pharmaceutical industry. Outsourcing and subcontracting can transfer risk of in-house failure or avoid committing internal resources. Switching options might become of great importance in the attempts to build new business models in the pharmaceutical industry. In general, switching option envisages the opportunity to reorient the production line either on the input side or on the output side.

Whereas all five types of options as shown in Box 4.1 may be of some relevance in the pharmaceutical industry, the analysis in the following focuses on abandonment options. With an abandonment option, the investor can decide to stop the project and "save" its follow-up expenditures, whenever the present value of the future cash flows of the project is not enough to cover the present value of its total (current

and future) staged investments, for example due to a decline of the sale price or in the product's expected market share. If there is a possibility to sell the abandonment project to others (or it may be switched to an alternative use) then not only can the follow-up expenditures be "saved" but a part of previous phases' expenditures will be recuperated. In this case, a "salvage" or "switch" value of the project implies that the option to liquidate is valuable. The project that can be liquidated with a positive salvage or switch value is worth more than the same project without such flexibility.

The "salvage" value of an R&D project depends on the intensity or specificity of the equipment used in the abandonment projects and on the importance of the research and development results already received. The value increases with each successful accomplishment of the project and the non-specificity of the utilized equipment. However, in the biotechnology industry, as in some other industries, the value of the same project may be different for different companies as noted by Borissiouk & Peli (2001): Firstly, a big pharmaceutical company has normally lower construction and marketing costs compared with a smaller company, i.e. economics of scale are involved. Secondly, compared to a new started drug company, the company that is already on that market may decide to purchase the developed drug, considering it as a "complementary" one in its current portfolio of products. Thus, economics of scale, other possible synergy effects and differences in risk perceptions may explain different price offers for an abandoned drug project among biotechnological firms.

At maturity (i.e. when no further delay of the abandonment decision is possible) the value of project is equal to the expected net present value of the future cash flows (*ENPV*) plus the value of the option to abandon the project (Smit & Trigeorgis, 2004):

$$Expanded\ ENPV = Static\ V + Max\ [abandon\ (S - V),\ continue\ (0)] \quad (4.1)$$

where S is the salvage or switching value. Thus, if $S > V$, then the project is abandoned; otherwise the project is continued implying that the option has no value.

In reality the salvage or switching value might be uncertain. Thus, if both the value of the underlying asset (V) and of the salvage value (S) are governed by some stochastic processes, then the option price valuation becomes much more complex. The complexity can however be significantly reduced if it is possible to express the value of one asset relatively to the other for all possible future contingent states. In this case the option value may be expressed as $max_s\ (E) = Max\ (V^s, S^s)$ where s specifies the possible states of nature (Smit & Trigeorgis, 2004). The decision rule basically implies that the project is continued whenever the project value is higher than the salvage value. However, if this ratio is becoming less than one in a given state, then the project is abandoned.

4.3.3. Real compound options embedded in vaccine development

The vaccine development project can be modelled as a compound option by looking at each investment stage as an option to accrue another option. The compound option nature of the vaccine development

process is illustrated in Figure 4.2. The project includes five investment decisions each of which might be looked upon as a real option. In the specific case, the five investments decisions are:

1) The decision to start the research phase in the beginning of 2010 which may be considered as the first compound option in the vaccine development project
2) The decision to make a patent application in the beginning of 2013 which may be considered as the second compound option
3) The decision to start the testing phase in the beginning of 2014 which may considered as the third compound option in the project
4) The decision to apply for approval of the vaccine in the start of 2016 which may be considered as the fourth compound real option
5) The decision to launch the vaccine in the start of 2017 which may be considered as the fifth and final compound real option in the vaccine development project

Thus, the use of options thinking implies that each time a specific development phase is finalized, it should be decided whether to invest in the subsequent phase (Yes) or (No), where the no decision means that the project is stopped.

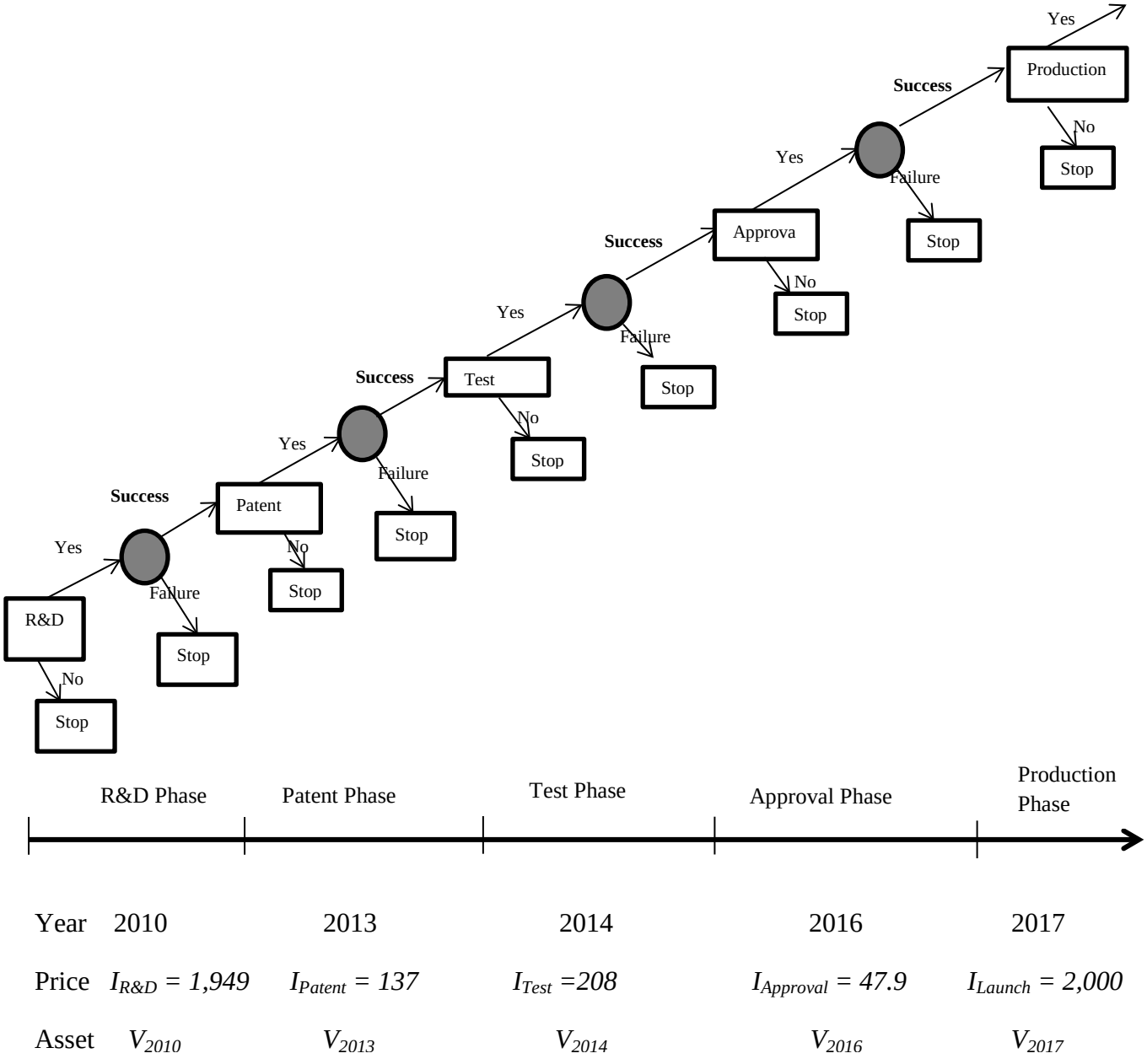
For reasons of simplicity it is assumed that all options are belonging to the European type of options, which means that the options can only be exercised at the end of each year during the development process. This assumption is however not very restrictive for a biotechnology firm where R&D projects typically are evaluated once every year as a part of the capital budgeting process for the coming year. From Figure 4.2 it is seen that both technological and economic uncertainties are embedded in the project.

The technological uncertainty is the risk of a failure in each project phase: In the research phase that no significant research results are obtained, in the patent phase that no patent rights are provided, in the testing phase that the vaccine agent is not biological effective or has some significant negative side-effects, and in the documentation and approval phase that the vaccine is not approved as a result of the regulatory review. The technological risks make the use of the compound options uncertain. For example, if it is decided to invest in the R&D phase, then this investment creates an option to invest in patent application if the research and development efforts turn out to be positive. However, if useless R&D results are obtained during the R&D phase, then the vaccine project becomes worthless and there is no opportunity to make a patent application. Therefore, the likelihood that the option of making a patent exists should be reduced with the probability of technological failure in the R&D phase.

The economic uncertainty, on the other hand, means that there is a right, but not a commitment, to make further investments after the completion of each development phase. The first option is acquired if it is decided to invest in R&D: A start of the R&D phase requires an investment of $I_{R\&D}$ as shown in Figure 4.2 which is the exercise price of the first option. Thus, if it is decided to invest in R&D, the option to make and submit a patent application arises. The value of the first option is not only

dependent on the expected cash flow from launching the vaccine in the future, but also on the flexibility to make investments in the subsequent phases of the development process in accordance with the future resolution of the technological and economic uncertainty.

Figure 4.2 Compound real options in the vaccine development



Year	2010	2013	2014	2016	2017
Price	$I_{R\&D} = 1{,}949$	$I_{Patent} = 137$	$I_{Test} = 208$	$I_{Approval} = 47.9$	$I_{Launch} = 2{,}000$
Asset	V_{2010}	V_{2013}	V_{2014}	V_{2016}	V_{2017}

The second option starts in the beginning of 2013 and expires when it is decided to invest in a patent application or to stop the project. The maturity of this option is by the end of 2013. The exercise price I_{patent} should be paid if it is decided to continue with development of the vaccine. In this case the exercise price also gives the right to the third option which is to make clinical and subclinical tests of the vaccine candidate. The value of the underlying asset – when the second option is acquired - is the cash flow from launching the vaccine, conditional on the decisions made with respect to the three subsequent phases of the project.

The third option starts with an investment in the test phase, which begins in 2014 and lasts three years. The exercise price of the option is I_{Test} which is the cost of making all the tests. If the option is exercised, it gives the right to a fourth option, which is to make a request for governmental approval of the vaccine candidate. In this phase the value of the underlying asset is again the cash flow from launching the vaccine, but now only conditional on two subsequent project development phases.

The fourth option begins in 2016 and last one year. The option is exercised by investing in assembling and submitting the test documentation and other relevant information to the governmental agency for approval. When this option is exercised a fifth option is consequently generated which is the option to launch the new vaccine. The exercise price of the fourth option is $I_{Approval}$ which are the investments made in submitting a request for approval of the vaccine. The value of the underlying asset of the fourth option is not only depending on the present value of the future cash flow from marketing the vaccine product but will also include the right to decide to proceed with the launch phase if the expected discounted cash flow in 2017 exceeds the associated investment costs (i.e. I_{Launch}).

The fifth and last option in the vaccine development process is the call option to launch the new vaccine product. The decision to launch will depend on whether the vaccine has been approved by the authorities, and secondly on the expected future cash flow at launch. It is assumed that the approval process takes one year which determines the maturity of the fifth option. The exercise price of the option is I_{Launch} which includes all the investments necessary to produce and market the new vaccine product. If the option is exercised then it is assumed that all cash flows generated by sale of the vaccine may be acquired. Thus, the value of the underlying asset at the time of launching the new vaccine is equal to V_{2017} as shown in Figure 4.2.

4.4. Valuation of real options

There are several approaches to estimate the value of real options. Valuation models based on the Black-Scholes and the lattice, especially the binomial-lattice model, approaches are among the most well-known and most utilized in both theoretical and real world applications.

4.4.1. The Black-Scholes formula

The Black-Scholes formula is the first and simplest formula for pricing options with finite maturities (Black & Scholes, 1973). The main advantage of the Black-Scholes model compared to other option

valuation methods is that only five inputs are required in the formula. As shown in Table 4.1, the five input variables required are the following: 1) the initial value (V) of the underlying asset, which in our case is the discounted value of the sales of the Campylobacter vaccine during its entire product life cycle; 2) the investment, or exercise price, (I), that is required to exercise an option (for example the investments required to exercise the option to launch a new vaccine); 3) the time (T) until maturity of the option (here the time until launch of the vaccine); 4) the risk-free rate of return (r); and 5) the volatility (σ) measured as standard deviation of the rate of return on the underlying asset.

Table 4.1: Mapping an Investment Opportunity into a Call Option

Investment opportunity		Variable		Call option
Present value of the underlying assets to be acquired	→	V	→	Asset price
Expenditure required to acquire the underlying assets	→	I	→	Exercise price
Length of time the decision may be deferred	→	T	→	Time to expiration
Time value of money	→	r	→	Risk-free rate of return
Riskness of the underlying assets	→	σ^2	→	Variance of returns on the asset

Source: Luehrman (1998a).

The Black-Scholes formula for the value of a call option without any dividend payments on the underlying stock may be written as:

$$C = VN(d_1) - Ie^{-rT}N(d_2) \quad (4.2)$$

where

$$d_1 = [Ln(V/I) + (r + 0.5\sigma^2)T]/\sigma\sqrt{T} \text{ and } d_2 = d_1 - \sigma\sqrt{T} \quad (4.3)$$

$N(d)$ is the cumulative standard normal distribution function. It is the probability that a normal distributed variable with mean of zero and a standard deviation of one would have a value less than d. "Ln" denotes the natural logarithm. In this expression, one of the most difficult parameters to estimate is the expected variance of the return on the underlying asset (σ^2). There is in principle an infinite number of economic factors that might influence the dispersion of the future value and hence return of the asset (including prices, quantities, capital investments, interest rates, inflation, etc.). In addition, there might be correlations between economic and technological uncertainties, e.g. technological resolution of uncertainty may reduce the economic uncertainty as well, and vice versa). In order to estimate σ, Copeland & Tufano (2004) suggest identifying the asset's value drivers, where one or a few key variables often constitute the most important. For a pharmaceutical company it may for example be the expected price of the new drug and/or the expected market share as assumed in e.g. Borissiouk & Peli (2001). Different Monte Carlo simulation techniques are widely applied to estimate the volatility parameter (σ^2) in real option valuation.

A transparent understanding of the Black-Scholes model is not easy. However, the first main term in (4.5) reflects the present value of the underlying asset, whereas the second term reflects the investment costs, discounted to the present date, and multiplied by the "risk-adjusted" probability, $N(d_2)$, measuring whether the investment costs actually will be incurred. It should be noted that in the Black-Scholes model the investment risk is accounted for in the probability of incurring the investment costs rather than in the discount rate which is the usual risk-adjusting approach adopted in traditional DCF analysis.

There are several general limitations associated with the Black-Scholes model. One of these is that the formula relies on the assumption of variance growing continuously over time or information arising evenly "every day". As further elaborated in the following section, this does not fit a typical R&D project where information tends to arise a discrete points in time, e.g. after a test or an experiment has been evaluated. Another limitation is that only European typed options can be evaluated. Third, it is implicitly assumed that the underlying asset value has a lognormal distribution, which implies that the rate of return on the underlying asset is normally distributed with a constant standard deviation over time. A fourth disadvantage, the above-mentioned lack of transparency and intuition means it also has the risk of becoming a "black box".

In particular two aspects restrict the use of the Black-Scholes model for valuation of R& D projects. The first is the requirement for complete financial markets in which a replicating portfolio can be constructed that reproduces (or, at least, is closely correlated with) the considered underlying real asset's payoff in all the possible states of nature (Brandão et al., 2005). Thus, it should in principle be possible to find a replicate portfolio, e.g. in financial or hedging markets, that provide information about the option value of the underlying asset. However, the characteristics and risks associated with R& D projects in general, and hence also projects dealing with development of new vaccines, are typically project specific and cannot be replicated in external markets. The lack of such a replicating portfolio implies that the markets are incomplete.

A second, and perhaps even more important limitation of the Black-Scholes model, is its inability to make comprehensive evaluation of compound options that is options on other options. As previously noted the development of a new Campylobacter vaccine may indeed be understood as a compound option, as investments in e.g. research activities generates subsequent options to e.g. submit patent applications and carry out clinical tests in the case that positive research results are obtained. An analytical solution to compound options might be provided by using the Geske approach, (Geske, 1979, Perlitz et al., 1999), which is an extension of the Black-Scholes formula.

4.4.2. Binomial option valuation

An important issue in real options valuations, and more generally in dynamic optimization problems, is how to model the development of uncertainty in prices over time. In real options valuation the dynamic development of the prices is modeled as stochastic processes. One of the most common stochastic

processes for diffusion of asset prices over time used in real options valuation, also in the Black-Scholes valuation model, is the Geometric Brownian Motion (GBM) process which can be written as:

$$dS/S = \mu dt + \sigma dz \quad (4.4)$$

where S represents the asset price, μ is the growth rate (drift), σ is the standard deviation of the returns (volatility), and dz is a Wiener process (Hahn & Dyer, 2011). The GBM process is modeling a continuously stochastic process of price developments requiring both analytically advanced and computationally complex solutions to stochastic differential equations.

Assuming continuous stochastic processes for price movements do however not necessarily reflect the real decision situations in many R&D projects.

Trang et al. (2002), among many, argue that new information that may influence the value of a project normally arises at discrete points in time. In case of R&D investments new information arrives typically at discrete points in time after some of the uncertainty has be resolved by carrying out specific activities. Therefore, managerial decisions related to such R&D projects are usually also taken at certain time points.

Assuming a one-year time period, the stochastic price development and therefore the real options valuation, is estimated using a binomial lattice approach in this study. The binomial lattice model for real options valuation was first introduced in Cox, Ross and Rubinstein (1979). Their model is recognised as an efficient discrete approximation to the GBM process because it is easy to apply, has an intuitive appeal and because it converges weakly to the Black-Scholes' (1973) model as the time periods (Δt) converge to zero. Furthermore, the binomial lattice model is flexible in the sense that a solution to American typed options can be obtained, whereas only European typed options can be evaluated by the Black-Scholes model. In contrast to the Black-Scholes and Geske approaches, the binomial lattice pricing model (two-state option-pricing model) is mathematically simple.

The use of the binomial lattice model to valuation of real options requires to steps:

- construction of an event tree of the underlying asset; and
- formulation of an optimization algorithm for exercising options in the tree.

Construction of the Event Tree

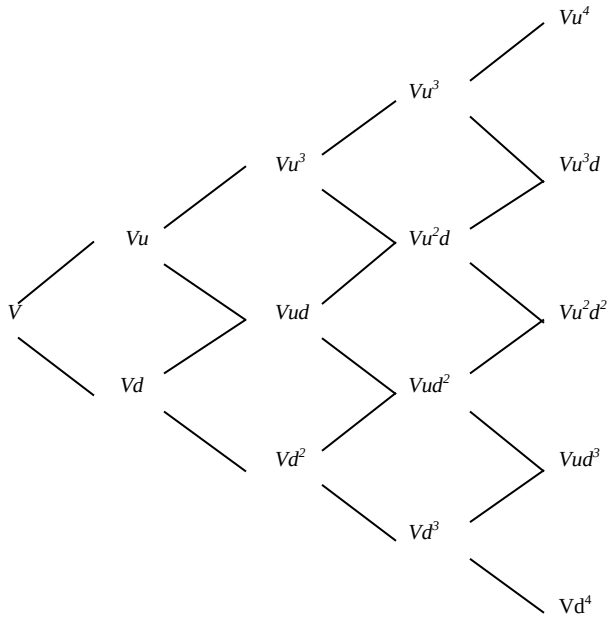
In the binomial lattice model there are only two states of nature which is an upward movement or a downward movement. Thus, in the first period the value of the underlying asset V may go up to Vu or down to Vd where u and d are some parameters to be estimated. Obviously, u and d specify the price process of the underlying asset. While not transparent in the use of the Black-Scholes model, a very explicit functional form for the price is assumed in the binomial model. In Cox, Ross and Rubenstein (1979) the up u, and down d, price movements are estimated as:

$$u = e^{\sigma\sqrt{\Delta t}} \quad \text{and} \quad d = e^{-\sigma\sqrt{\Delta t}} \tag{4.5}$$

where σ is the annual volatility and Δt is time interval between price changes determined as Δt = T/n where n is the number of periods [4].

In Figure 4.3 is shown a generic binomial lattice tree including five stages. By allowing for a sequence of periods with such binomial movements, a large set of paths (a binomial "tree") may be constructed that approximates all possible value changes that could occur to the underlying asset during the life of the option.

Figure 4.3: A binomial lattice tree

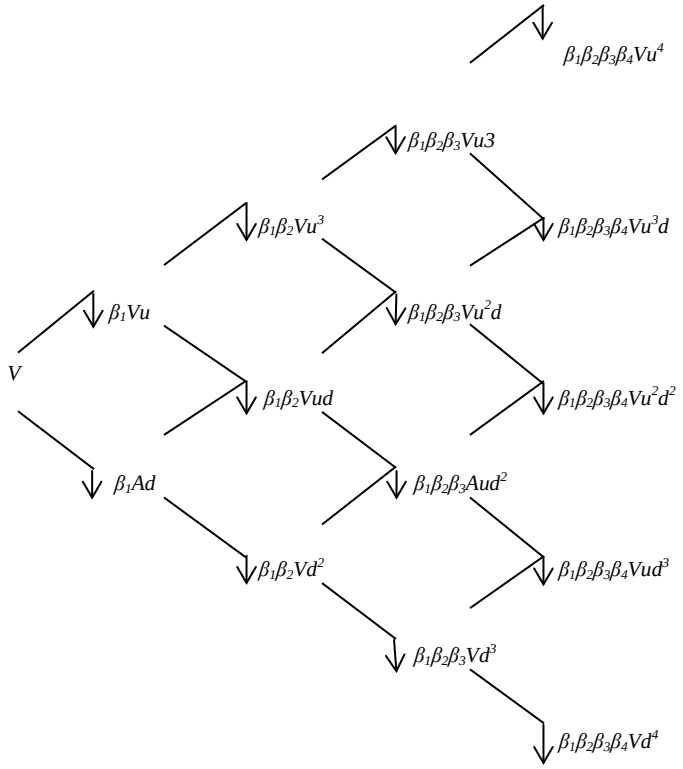


As illustrated by Trang et al. (2002), it is possible to include the impact of the technological uncertainty, which is unique to the specific R&D project, into the binomial tree. The technical probability of success in any phase of the R&D project can be considered as equivalent to decreasing the value of each node proportionally to the probability measure as shown in Figure 4.4. The β_i's in Figure 4.4 measure "the probability of success" in stage *i* of the project. Thus, if for example the probability of technical success is 50 pct. in stage 1 and 30 pct. in stage 2, then the potential value of the underlying asset in all nodes in stage 2 should be reduced by the factor $\beta_1\beta_2$ or 0.15. It reflects that the technical project uncertainty is only resolved after it has been decided to carry through a certain phase of the project, implying there is no flexibility value associated with a "wait-and-see" strategy. The implicit assumption made in this approach is that the technological risks in the project are uncorrelated with the market risks (i.e. the $(u_i.d_i)$'s are independent of the β_i's). As noted previously

[4] For a complete discussion of the assumptions used in this approach, see Rendleman & Bartter (1979).

this may not always be the case. Thus, the technological uncertainty does not affect the value of the project as such when it is independent of the economic uncertainty. However, if the project fails technologically in any stage (with the probability $(1-\beta_i)$) then the entire project value drops to zero. As a result the technical uncertainty decreases the expected value of the project (and of the embedded options in the project).

Figure 4.4: A technological risk-adjusted binomial tree



The binomial lattice tree is a "recombining" tree which is an important feature in order to reduce the number of computations in case of many periods and many nodes. The binomial tree is combining by the fact that the upward movement (u) always is the inverse of the downward movement (d), i.e. $u = 1/d$. Thus, at each stage there are $N+1$ nodes and not 2^N as in the case of a binomial tree that is not recombining.

A disadvantage of the binomial lattice model, on the other hand, is that the (GBM) stochastic process is not mean-reverting over time (i.e. implying that values above average tend to be followed by values below average and vice versa). One of the most important driving factors for the volatility of R&D projects is probably the actual market price of the developed product or service. According to Hahn and Dyer (2011) several studies of historical and future data have found that mean-reverting processes often

are the best models for describing the behaviour of commodity prices. Thus, if vaccine prices and other major project risks indeed are mean reverting, then the application of an approximate lognormal geometric Brown diffusion model may significantly exaggerate the uncertainty in the cash flows from the project and thus overestimate the options values.

Formulation of an optimization algorithm for exercising options in the tree

The value of the project including the embedded options is estimated by starting at the end of the binomial-lattice tree and then moving backwards. The value of the project at each node in the final stage n can be written as:

$$V_{n,k} = \begin{cases} Vu^{n-k}d^{k} - I_n \;\; if \;\; Vu^{n-k}d^{k} - I_n > S_n \\ S_n \qquad\qquad otherwise \end{cases} \tag{4.6}$$

where

$V_{n,k}$ is the discounted value of the project in the final stage n at node k

$k = 0, 1, \ldots, j$. $k = 0$ is equal to the top node; $k = j$ corresponds to the bottom node.

I_n is the total investment cost necessary for launching the vaccine product, i.e. the exercise price of the decision to launch

S_n is the salvage value of the project if it is decided not to launch the vaccine.

Thus, if the developed vaccine is launched in stage n (i.e. the final stage in the R&D process) then the project value is equal to the present value of all future net cash flows during the remaining product life cycle minus the required costs to launch the vaccine (i.e. investment and marketing costs). On the other hand, however, if it is decided not to launch the product in the last stage, then the value of the project is just a salvage value which might eventually be zero or even negative. Thus, the decision to launch or not launch is equivalent to an exercise decision on a real option. New abandonment options may however exist at previous stages, $n = 1, 2, \ldots, n-1$ in the binomial tree if it would be decided to exercise the real option in the stage n. In this case, these options have to be evaluated as compound options. However, if there are no options connected to a given stage, then the value of the project in that stage is just discounted over the time period Δt.

Two different backward algorithms for solving the binomial lattice tree for the stages *n = 1, 2, ….., n-1* are available. One approach involves finding the option value at each node by first estimating the replicating portfolio and then secondly evaluating whether the option value is greater than the exercising value at that node. Using the replicating portfolio algorithm to solve the binomial lattice tree and hence identify the project value (including the embedded real options) is for example used in Copeland and Tufano (2004). While the replicating portfolio method provides a market-based correction for the risk in the project, the calculations are rather cumbersome since they have to be repeated at each node (Brandão et al., 2005).

Another method is to use the risk-free interest rate as the discounting factor and then account for project risk by adjusting the probabilities for up and down changes in the asset price, respectively. This method has been adopted as it is equivalent to the replicating portfolio method but simpler to apply in the estimations. When the up's and down's are estimated $u = e^{\sigma\sqrt{\Delta t}}$ and $d = e^{-\sigma\sqrt{\Delta t}}$, respectively, then the risk neutral probability of an upward movement can be estimated as (Cox, Ross and Rubenstein, 1979):

$$p = \frac{e^{r\Delta t} - d}{u - d} \tag{4.7}$$

where $p = [(1+r) - d]/(u - d)$ when $\Delta t = 1$ and $r \rightarrow 0$. Sometimes p is called a risk-neutral probability as it is the probability that would be applied in decision making, where investors are indifferent to risks, i.e. they have a risk-neutral attitude (see e.g. Smit & Trigeorgis, 2004).

In order to estimate the option value of the entire project it is necessary to calculate the option value at each node in the binomial tree (minus the nodes in the final stage) by using the risk-neutral probabilities and using the risk-free interest as the discounting rate. This is accomplished by deciding at each of these nodes (*where j, k ≠ n*) whether to continue or abandon the project. The option value of the decision in node *k* at stage *j* can be calculated as:

$$O_{j,k} = max\ \{\beta_j[O_{j+1,k}p + O_{j+1,k+1}(1-p)]e^{-r\Delta t} - I_j\ ,\ S_j\} \tag{4.8}$$

where $O_{j,k}$ is the option value of project at stage j and node k at that stage, and I_j is the investment cost necessary to continue the project at stage j, e.g. R&D investments, testing cost etc.

It should be noted that equations (4.6) and (4.8) evaluate compound options in a staged investment project. If there are opportunities to affect the future value of the project in other ways than just abandoning the project, e.g. by switching the inputs or output or making delays in the project etc., as described in section 4.3.2, these real options have to be included. For example, if an option exists at some stage after the launch of the Campylobacter vaccine to expand the production and marketing

capacity in order to capture new market sale opportunities, then the value of this expansion option (see the explanation of this option in section 4.3.2) should be added to equation (4.8) in the following way:

$$O_{j,k} = max \ \{\beta_j[O_{j+1,k}p + O_{j+1,k+1}(1-p)]e^{-r\Delta t} - I_j + max\ [ENPV\ of\ expansion\ (\varepsilon V - I_E),\ 0],\ S_j\} \qquad (4.9)$$

If, however, additional compound options have been identified, for example as opportunities to develop and sell some related vaccines, then these compound options should be evaluated according to (4.8) and (4.9) and added to the option value of the original vaccine project.

By adopting decision-tree and binomial-lattice methods, Kellogg & Charnes (2000) compare the value of a biotechnology company (Agouron) with the sum of the values of its drug development projects. The computed values of Agouron are compared to the actual market values at specific points in time during the development of a new drug used to treat HIV-positive tested patients. Values for Agouron were also found using a binomial lattice with the addition of a growth option, which was added because the development of an initial new molecular entity (NME) is similar to purchasing a call option on the value of a subsequent NME. These modelling approaches may also be integrated with other quantitative methods. As explained later, Monte Carlo simulation is an especially powerful tool to estimate the volatility of the underlying asset in an option evaluation framework.

4.4.3. Valuation of the compound option

In this section the valuation of the compound options associated with the development of the new Campylobacter vaccine is estimated.

A volatility of 35 per cent, (σ=0.35), is assumed for the underlying asset. According to Trang et al. (2002), a volatility level in the range of 30 to 40 per cent is believed to be common in the pharmaceutical industry. σ-values of a similar size are used in Kellogg et al. (2000) and Perlitz et al. (1999). When the time between price changes is assumed to be 1 year, $\Delta t = 1$, then $u = e^{0.35\sqrt{1}} = 1.4191$ and $d = e^{-0.35\sqrt{1}} = 0.7047$.

If we assume that a high-price strategy (which is calculated to be the most profitable in the model presented in chapters 2 and 3) will be pursued in the marketing phase, the expected gross present value (GPV) for the EU-27 scenario is calculated to be 14.7 million €. This figure is based on the discounted value in 2010 of the expected gross margin from the sale of Campylobacter vaccines in the period 2017-2027. The estimated sales price is about 2 eurocent per dose sold and the variable production costs and distribution costs are estimated to 0.8 and 0.5 eurocent per dose, respectively.

By using the calculated expected discounted gross value of the production and sale of the vaccine as well as the determined “up” and “down” factors, it is possible to compute the expected outcomes of the underlying asset (GPV) at each stage in the development process as shown in Table 4.2. The event tree is constructed by multiplying GPV (14.7 million € in the EU-27 scenario), with the up-factor of 1.4191 and the down-factor of 0.7047, respectively. This multiplication procedure is repeated in each stage

until the end of the launch stage. It should be noticed that the expected values of the underlying asset shown in Table 4.2 have not been adjusted for the risk of technological failure in each stage of the development of the vaccine product.

Table 4.2: Event tree for the Gross Present Value (GPV) of the Campylobacter vaccine development project (million €)

Staged investments	Research phase			Patent	Testing		Approval	Launch
	2010	2011	2012	2013	2014	2015	2016	2017
	14.7	20.8	29.6	42.0	59.6	84.5	119.9	170.2
		10.4	14.7	20.8	29.6	42.0	59.6	84.5
			7.3	10.4	14.7	20.8	29.6	42.0
				5.1	7.3	10.4	14.7	20.8
					3.6	5.1	7.3	10.4
						2.6	3.6	5.1
							1.8	2.6
								1.3

Construction of the Option Tree

As described in previous chapters, the development and marketing process of the Campylobacter vaccine can be considered as a sequence of five investment decisions. By investing in the R&D phase, the decision makers acquire in exchange the option to continue with the next phase of the project. Thus, exercise prices (I) are specified as the "staged" investments in the binomial lattice model as shown in Table 4.3.

Table 4.3: Investment phases in the Campylobacter vaccine development

Phase	**Start**	**Length of period**	**Investments, 1000 €**	**Unconditional Success Probabilities (Prob)**
R&D[1]	2010	3	1,949	20%
Patent	2013	1	137	75%
Test[2]	2014	2	208	20%
Approval	2016	1	48	90%
Launch	2017	10	2,000	

1) The research investment is equally divided between the three years and the annual success probability is estimated to be 58 per cent
2) The testing investment is equally divided between the two years and the annual success probability is estimated to be 45 per cent

The option tree of the project is shown Table 4.4. The option tree integrates the optimal decisions that will be taken at each stage (period) and each node (indicating the possible development of the value of the underlying project). The value at each node is contingent on:

- the state of nature (up or down driven by economic uncertainty)
- the compound investments
- the probability of technological development success (the technological uncertainty)

The calculations start at the end of the option tree with the computation of the payoffs (Max_{2017}), which is based on the last column of Table 4.2. These payoffs are obtained from applying equation (4.6) which is equal to $Max_{2017}\,[V_{2017} - I_{Launch};\, 0]$ for all nodes in that stage (assuming that the salvage value of the project in the launch stage is 0). Hence, if the vaccine candidate is approved, then there is an option to invest in the launch costs and obtain the right to the future cash flow from selling the vaccine in the market during the entire product life cycle. The launch costs are estimated to be 2 million €. Thus, if the option is exercised then the expected value of the option is the present value of the future gross margins from the production and sale of vaccine minus these launch cost. For example, in this first node the decision problem is $Max_{2017}\,[170.2 - 2;\, 0] = 168.2$ implying that the option should be exercised. However, in case this value is becoming negative, then it is better to leave the launch phase option unexercised. The abandonment of the project at that time makes it possible to save the launch costs. The possibility to abandon and thus save the launch costs is incorporated in the computation of the option values by defining the Max_{2017} payoffs as the maximum of the net value of the underlying asset or zero.

Table 4.4: Option tree for the Campylobacter vaccine development project (million €)

Staged investments	Research phase			Patent	Testing		Approval	Launch
	2010	2011	2012	2013	2014	2015	2016	2017
	0.0	0.0	1.4	5.2	10.2	33.1	106.2	168.2
		0.0	0.2	2.3	4.8	16.0	51.8	82.5
			0.0	0.9	2.1	7.5	24.8	40.0
				0.2	0.8	3.3	11.4	18.8
					0.2	1.2	4.8	8.4
						0.2	1.4	3.1
							0.2	0.6
								0.0

These values serve as the underlying values of the other compound options that are included in the development of a Campylobacter vaccine. The values of these options are estimated by use of equation (4.7) and (4.8). The risk-neutral probabilities for an up (p) and a down (1-p) are calculated by (4.7) as $p = (e^{0.02x1} - 0.7047)/(1.4191 - 0.7047) = 0.4413$, and $(1-p) = 0.5587$.

By using equation (4.8) the exact equation for estimating these option values for approval of the Campylobacter vaccine in each node at the time stage 2016 is (again assuming that the salvage value of the project is 0 in this stage):

$$O_{2,k} = \beta_j\,(p*MAX_{2017up} + (1-p)*MAX_{2017down})(1 + R_f)^{-1} \qquad (4.10)$$

which may be interpreted as a type of certainty equivalent that is discounted with the risk-free discount rate. As an example, calculation of the Max value in the first node in column Max_{2016} is calculated as

$O_{2,1} = 0.9(0.4413*168.2 + 0.5587*82.5)\ (1.02)^{-1} = 106.2$ *million €*, where 0.9 is the success probability of approval of vaccine by the regulatory authorities. Thus, the decision rule for exercising the option at the first node at time stage 2016 is:

$Max_{2016}\ [O_{2,1} - I_{Approval};\ 0] = Max_{2016}\ [106.2 - 0.048;\ 0] = 106.2$ *million €*

where $I_{Approval}$ is the investment cost to submit the application for approval of the vaccine.

Employing this method for all nodes at all stages in the event tree and each period, the exercise values are rolled back to the first stage, obtaining $Max_{2010} = 0$ as shown in Table 4.4. Thus, the net present value of the project including the compound options values to abandon the project in the different development stages is zero. Therefore, there is no positive economic value of the project taking into account the managerial flexibility in conducting the development process and stopping the project if the market conditions turn out to be unfavourable. Compared with the results presented in table 3.9, the real options approach yields a more positive result than the pure probabilistic approach, because it restricts the NPV to be non-negative. On the other hand, the still probabilistic elements of the real options approach implies a less positive outcome than the "optimistic" approach presented in table 3.9, because it still takes into account the probability of lower positive outcomes.

One important reason for this result is that the joint probability for a technical success of the project is below 3 per cent (estimated from the unconditional success probabilities shown in Table 4.3). In case of a positive project value including the compound options the flexibility to abandon the project might be computed according to the following formula:

Flexibility value = Value of the Project including flexibility – Value of the Project excluding the flexibility (4.11)

where the latter is the value of the project obtained by using the ENPV method.

4.4.4. Valuation of additional options

As shown in the decision tree for the development of the Campylobacter vaccine (section 2.2) there exist some opportunities to sell the vaccine candidate conditional on good R&D results, accepted patent application and positive evidence obtained from the clinical testing. These opportunities are however not real options per se as there are no ways to make an exercise decision and thus resolve the uncertainty associated with the expected profit from the sale of the vaccine candidate.

One way to transform these sale opportunities into a real options framework would be to assume that the investment to submit an application for official approval of the vaccine could instead be invested to resolve whether it is possible to sell the not yet approved vaccine candidate to another company at a

high or low profit conditional on obtaining positive testing evidence; and by assuming that the investments in testing – or at least part of these investments – alternatively could be invested in resolving whether it is possible to sell the untested vaccine to another company at a high or low profit conditional on an accepted patent application; and finally assume that investments in a patent application alternatively could be invested to resolve whether it is possible to sell the unpatented vaccine candidate to a high or low profit conditional on positive R&D results. In this case the investment costs might be understood as exercise prices for exercising the options to sell the vaccine candidate if successful R&D results are obtained, or a patent is granted or positive testing evidence is realized.

Thus, the three exercise prices are: I_{S1} = 137,000 € (sell the vaccine if obtaining positive R&D results), I_{S2} = 104,000 € (sell the vaccine if granted a patent certification; and assuming that the exercise price is half of the total testing costs), and I_{S3} = 47,928 € (sell the vaccine if positive testing evidence is assumed).

The options values for the three sale opportunities can be estimated from the event tree in Table 4.2 and the information concerning the technical success probabilities etc. Consider the first option to sell after a successful R&D phase, which is assumed to take place in 2013. Thus, conditional on the first project value in 2012 (i.e. 29.6 in Table 4.2), the option value from selling the vaccine candidate in 2013 can be estimated as $O_{S1,1} = 0.2(0.4413*42 + 0.5587*20.8)\ (1.02)^{-1} = 5.8$ *million €,* where 0.2 is the success probability of good R&D results.

Thus, the decision rule for exercising the option to sell the vaccine given the first node in 2013 is $Max_{2013}\ [O_{S1,1} - I_{s1};\ 0] = Max_{2013}\ [5.8 - 0.137;\ 0] = 5.8$ *million €,* where I_{s1} is the investment cost to exercise the sale option instead of investing in a submission of a patent. Using the same method the option values for selling the vaccine in 2013 conditional on the two other project values in 2012 can be calculated to $O_{S1,2}$ = 2.8 million € and $O_{S1,3}$ = 1.3 million €, respectively. The same algorithm can be applied for the sell options if either patent is granted (O_{S2}), or if good test results are obtained.

These option values for selling the vaccine candidate can be used in calculating the value of the total project, including now both the options to abandon the project at different stages and the options to sell the vaccine, by use of equation (4.8), but where the salvage value S is not set to zero as before, but now is set equal to the option values of selling the vaccine candidate in case of either positive R&D results, receiving a patent or in case of positive testing evidence. Thus, the decision rule for exercising the option at the first node at time stage 2016 is now $Max_{2016}\ [O_{3,1} - I_{s4};\ S_{3,j}]$, where $S_{3,j} = O_{3,j}$ is the expected sale profit in node j from selling the vaccine candidate if positive testing evidence is obtained.

Using the estimated salvage value (i.e. profit estimates for selling the vaccine candidate) we get the option tree shown in Table 4.5. It is seen that the value of the project is now 1 million euro. Comparing Tables 4.4 and 4.5 it becomes clear that the value of the project has increased significantly in the phases preceding the approval phase by including the sell options.

Table 4.5. The option tree for the Campylobacter vaccine development project including the options to sell the vaccine (million €)

Staged investments	Research phase			Patent	Testing		Approval	Launch
	2010	2011	2012	2013	2014	2015	2016	2017
	1,0	2,4	5,8	6,2	10,3	33,2	106,2	168,2
		1,2	2,8	3,0	4,9	16,1	51,8	82,5
			1,3	1,4	2,2	7,5	24,8	40,0
				0,6	0,9	3,3	11,4	18,8
					0,4	1,2	4,8	8,4
						0,3	1,4	3,1
							0,2	0,6
								0,0

Using the probabilities determined in expression (4.7), and linking these in different years, it is possible to associate probabilities with each of the outcomes in the option trees in tables 4.4 and 4.5. For example, the probability of the upper outcome in 2011 in table 4.5 (=2.4) equals 0.4413, and the probability of the second outcome in 2012 (=2.8) is equal to 0.5587*0.4413 + 0.4413*0.5587=0.4932, etc. Associating these calculated probabilities with the different outcomes in the two option trees, it is possible to estimate probability-weighted outcomes at different phases in the two option trees. These probability-weighted outcomes can be compared with the outcomes in the direct and probabilistic decision trees in Table 3.8, and this is done in Table 4.6.

Table 4.6. Expected profits (NPV) (1,000 €)

	Strategy/perspective		Real option	
1,000 €	Direct	Probabilistic	Without sales option	With sales option
R&D	10,803	-1,938	0	999
Patent	12,752	89	1,565	2,076
Test & documentation	12,877	391	2,258	2,268
Production and distribution	13,062	8,655	12,978	12,978

A number of observations emerge from this table. First, it is noteworthy that all weighted outcomes in the option trees are non-negative and higher than the corresponding figures in the probabilistic decision tree. Second, the probability-weighted outcomes in the option trees converge towards the outcome of the direct ("smart-and-lucky") branch of the decision tree, along the phases. Third, the probability-weighted outcomes become higher when including sales options than without including these options.

5. Discussion

The cost analyses in the previous chapters suggest that the development, production and marketing of a Campylobacter vaccine involves different types of costs which have to be paid if the use of such a vaccine should be adopted in commercial broiler production.

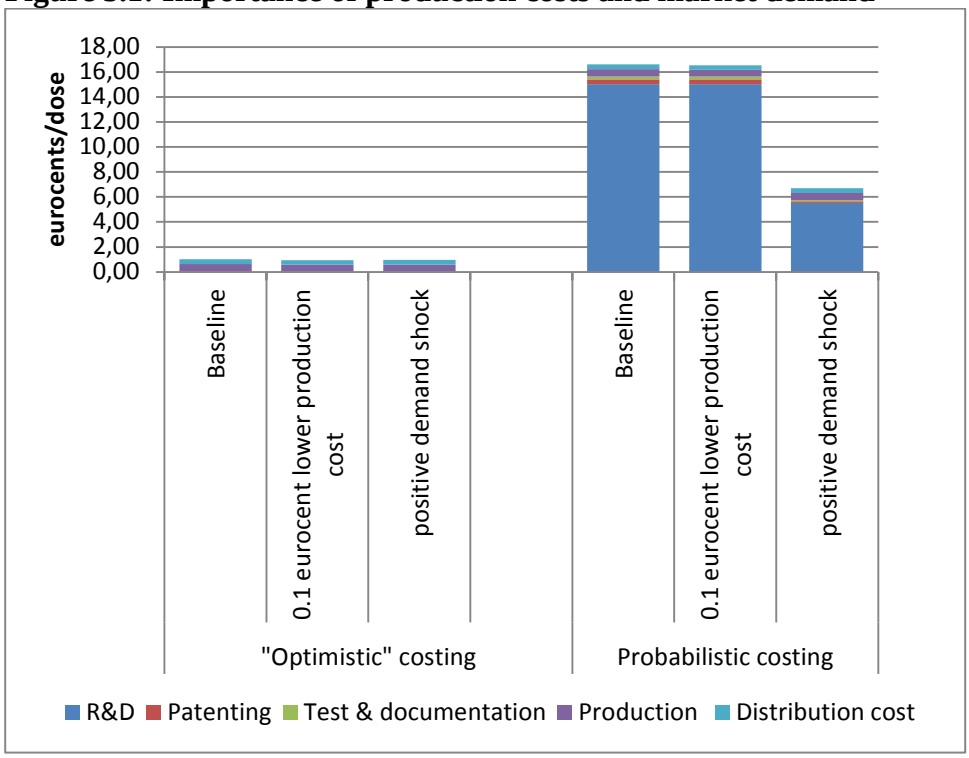
5.1 Critical factors in the costs of veterinary vaccine development

The cost analyses are however based on a number of assumptions, of which some can be considered as uncertain to various extents. Due to the nature of the issue, such as fierce competition within the pharmaceutical industry, the amount of publicly available data on costs of vaccine development and production is very limited. Hence, the empirical foundation for the cost assumptions used remains rather weak. Costs related to research, development and testing have been estimated on the basis of collaboration with researchers in these fields in order to obtain reasonable estimates of personnel and laboratory costs related to such development projects. On the other hand, specific cost data related to manufacturing and distribution of such products are considered much more commercially sensitive, and therefore these have been estimated by backwards calculation from market prices of similar types of vaccine products on the market.

Furthermore, the estimated market potentials underlying the calculations are also subject to considerable uncertainty. In the analysis, we have based the estimation of these market potentials on the number of broilers produced and an assumption that the demand for Campylobacter vaccine is positively related to the size of the gross margin in broiler production, using three alternative delimitations of the market. However, although such assumptions appear reasonable, it should be recognized that there is hardly any evidence for the specific quantitative relationship between broiler production and potential demand for this vaccine.

Other important assumptions for the cost calculations, which are also subject to uncertainty, include assumptions of the discount rate and the time frame for the respective phases in the vaccine development process. Nevertheless, the estimates of market potential and unit costs of manufacturing and distribution constitute the key factors for economic viability of the vaccine development (Figure 5.1).

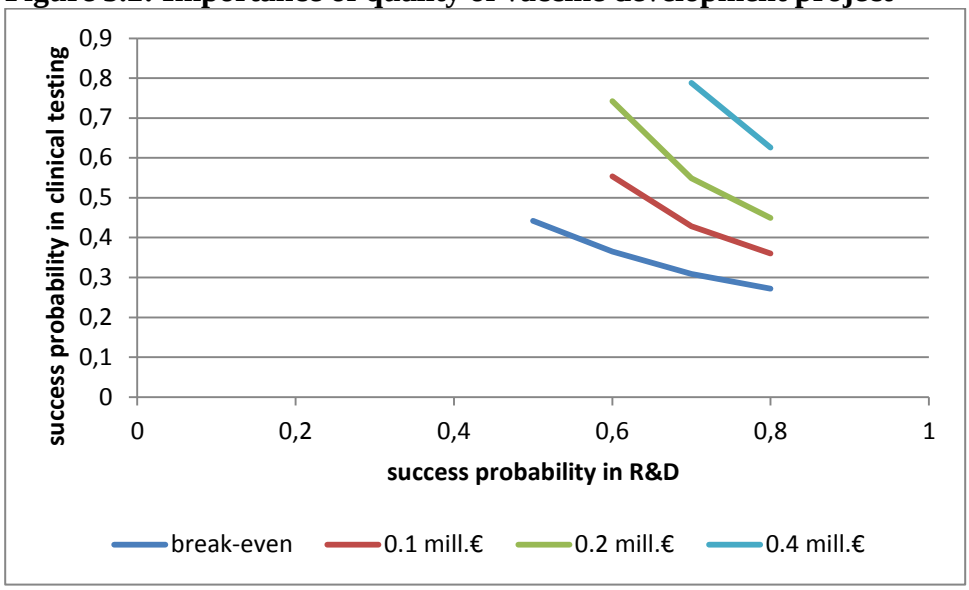
Figure 5.1: Importance of production costs and market demand



The above-mentioned uncertainties apply to both the deterministic and the probabilistic analyses of costs. Furthermore, the outcomes of the calculations based on probabilistic modelling and real option valuation are also highly dependent on the applied assumptions of probabilities of success and failure in the different phases, which must also be considered as highly uncertain. In the calculations, especially the assumptions of an expected 20 per cent success rate in a new R&D project and the assumption of an expected 20 per cent success rate in clinical testing are critical. Higher expected success rates in these project stages will improve the economy of the project considerably. Figure 5.2 illustrates the importance of these two success rates for the profitability of the entire project in a real options setting in terms of iso-profit curves for different levels of profit.

These sensitivity analyses point at the importance of production costs and marketing opportunities as well as the quality of the vaccine candidate (in terms of expected success probabilities) as critical factors for the economic success of a vaccine development project.

Figure 5.2: Importance of quality of vaccine development project



In relation to decision making, the considerable sensitivity of results to these factors suggest a considerable uncertainty in the quantitative estimates to be derived from analyses such as the one presented in this report. Nevertheless, quantitative calculations like these illustrate the importance of different factors and some relative magnitudes of the costs in different phases of the development process which are important determinants for decision making in business management in pharmaceutics as well as in decisions regarding public policy, including agricultural policy and health policy.

5.2. Implications for business

Marketing a Campylobacter vaccine for broiler production has mainly implications for the pharmaceutical and biotechnology industry, for veterinarians and for the agricultural sector.

For the pharmaceutical industry and the biotech firms, the incentives are primarily profit as the companies are assumed to be owned either by private owners or by investors who demand a competitive return on their investments in the long run. As the above results suggest a relatively low profitability in the development of a Campylobacter vaccine to broilers, investors' request of profit may constitute a barrier for such development to take place. The industry's economic incentive to undertake investments in the vaccine developments would be rather limited. The lack of incentives to invest in the research has to do with the fact that it is difficult to develop and accredit new vaccines (Frank & Griffin, 2002). A central part of the development is the costly field studies that are carried out to validate and test the vaccine efficacy. Variation in the efficacy found under different field conditions may threaten the registrability of a vaccine for animal use. Extensive field trials are required because the available experimental infection models have some limitations. The sensitivity analyses however

indicate that the profitability of such a project could be enhanced if the vaccine candidate has a high quality, i.e. relatively close to being ready for testing and with a relatively high probability of passing the necessary testing procedures.

Farmers are also assumed to be driven mainly by profitability when deciding whether or not to pay for vaccine for their chicken herds and whether to comply with requirements to present their animals for vaccination. European broiler farmers are in general facing rather fierce price competition on the international markets, implying that net margins in broiler production is relatively low. Hence, farmers have relatively little economic incentives to take up the extra cost of vaccinating the broilers as such additional cost may turn a small positive margin into a negative one, unless they are compensated by obtaining a higher price upon delivery to slaughtering.

Although the farmers are influenced by the veterinarian service, they are still responsible for the animal welfare and health (McLeod & Rushton, 2007). Even though the veterinarians have their own private incentives, they also share incentives with the farmer regarding the most profitable animal production under the legislative framework regarding e.g. animal welfare. For several reasons, the veterinarian service is assumed to have incentives to save the use of medicine in the animal production by advising in the use of a vaccine if such vaccination has significant health benefits and is available at a feasible cost. A secondary task is that veterinarian often has a duty to notify the farmer to the veterinary authorities if animal health and welfare rules are not fulfilled. This may cause a conflict between farmers and veterinarians.

5.3 Policy implications

Although the economic incentives to undertake investments in the development of a Campylobacter vaccine may be relatively limited from a business economic perspective, society may still have an interest in such a vaccine, because it can prevent the spreading of Campylobacter from animals to humans and thus save costs for the society.

Hence, the development of such vaccines might possibly be supported by the public society if the political decision is to reduce the health costs regarding Campylobacter. The European Technology Platform for Global Animal Health under the European Commission has prioritised Campylobacter highly among the group of food borne zoonoses as major areas for public funded R&D. For example, this is recommended in the “Strategic Research Agenda” by the stakeholders of the industry under the IFAH Europe (the International Federation for Animal Health - Europe). These recommendations are made to accelerate the development of the most effective tools for controlling animal diseases of major importance to Europe and the rest of the world (IFAH-Europe, 2005).

In many cases the veterinary pharmaceutical industry develops vaccines in cooperation with universities, R&D institutes and other bodies. The chosen stakeholders include the pharmaceutical

industry or biotech firms, veterinarian service, farmers and the universities (R&D), the government and the general public – each with potentially different economic incentives.

A part of the public finance from the society goes to the R&D at the universities basically prioritised by the politicians. Besides the number of educated students, the universities are also awarded in regards to how many new research results they produce, e.g. in terms of patents. Therefore, although universities' incentives are not pure profit as for the commercial companies, they still have very strong interests in the development of e.g. new vaccines to secure grants and donations from the society also in the future.

The industry is assumed to have incentives to extract the results and knowledge from the universities' R&D work. A key issue is who benefits from the universities' research and development, and who buys and commercialises the patent rights of e.g. a new vaccine. Such issues may pose a barrier for the utilization of new discoveries and may also lead to additional transaction costs in the process from discovery to commercialisation.

The public and the government are assumed primarily to be aware of the potential production loss because of people getting ill of Campylobacter and the direct hospital costs caused by the disease. But also the potential lack of future income from exports if the demand decreases in a longer period due to disease risk may be a concern for the public at large. Such incentives could drive the government to decide whether to encourage, permit or ban the use of vaccination or make it compulsory for the farmers. A study by Jensen & Jensen (2013) concludes that a compulsory Campylobacter vaccination programme in the European Union would lead to benefits (in terms of avoided cost of illness from lower productivity of labour) in the area of 1.24-1.80 eurocents per dose, depending on whether such a programme would be accompanied by a ban on broiler imports from other parts of the world.

A reduction in the cost of illness due to e.g. Campylobacter could be considered as an external benefit. Despite the overall potential for vaccines as a cost-effective technology, the pharmaceutical companies have in general only low investment in the development of new veterinary vaccines, because they do not reap the external benefits of improved public health (or only a small share of this benefit).

A policy implication of this situation could be that a Campylobacter vaccination programme should be supported by the government, for example by subsidizing the investment in research to develop such vaccines or by subsidizing the running costs of vaccination at the farm level, for example to distribute the vaccine to slaughter companies at a subsidized price, for them to distribute to the farmers with a requirement to use the vaccine. However, for such a public intervention to be successful, it is crucial that a vaccine can be developed at a cost that does not exceed the benefits, including the externality benefits, to be derived from the vaccine.

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EMA-2: European Medicines Agency: Guideline on Good Clinical Practices (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004343.pdf)

EMA-3: European Medicines Agency : Guideline on the conduct of bioequivalence studies for veterinary medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105372.pdf)

EMA-4: European Medicines Agency: Guideline on statistical principles for veterinary clinical trials for veterinary medicinal products (pharmaceuticals) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/01/WC500120834.pdf)

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