Putting a price on life

Approaching a sustainable model for pricing hospital medicines in Denmark

Master's thesis
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Dan Lin and Kasper

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1 Abstract

The subject of medicine pricing has received much attention due to new medicines being introduced at record prices, as well as sudden price hikes of already marketed medicines, challenging medicine budgets across the world. Denmark is no exception, as the costs of sourcing medicines for the Danish public healthcare system have doubled from 2007 to 2017. In light of the recent introduction of the Danish Medicines Council, the objective of this paper is to recommend sustainable policy recommendations on the pricing of hospital medicines in the Danish public healthcare system. This paper takes a holistic approach, considering payer affordability, patient access to medicines and the effects on private pharmaceutical research and development simultaneously. This paper explores the topic through an analysis of the Danish public healthcare system, where five challenges were identified. To solve the challenges, findings from primary research conducted through twenty expert interviews were analyzed, along with an exploration of existing literature on three pricing models: value-based pricing, profit control and external reference pricing. The paper proposes seven specific recommendations based on the three pricing models. While no one model is perfect in insolation, this paper finds value-based pricing to be the most sustainable model, with profit control and external reference pricing only providing some niche uses.

2 Introduction

The price of medicines is a topic that has received much attention over the last few years. In the United States, the largest market for pharmaceuticals, rising costs of many medicines became a vocal topic for the former presidential candidate Hillary Clinton during the 2016 election campaign (Reuters, 2016). Martin Shkreli became infamous as his company, Turing Pharmaceuticals, acquired the rights to sell the medicine Daraprim, and subsequently raised prices abruptly from 13.50 USD to 750 USD per pill, earning Shkreli the nickname "the most hated man in America" (Thomas and Swift, 2017). Canadian pharmaceutical company Valeant received similar attention for its price hikes, with its pricing practices being dubbed as "predatory" by Clinton in a campaign ad (Mukherjee, 2016).

Beyond sudden price hikes of already marketed medicines, new medicines are also being introduced at record prices, challenging the budgets of payers across the world. As an example, the medicine voretigene neparvovec-rzyl, marketed as Luxturna for the treatment of retinal dystrophy, costs 850 thousand USD (about 5.3 million DKK) per year (Kaltenboeck and Bach, 2018). Being unable to afford the latest medicines was previously reserved for developing countries, but recently, wealthy developed countries have had to come to terms with the necessity of prioritizing medicines (Kieny, 2016).

In Denmark, the topic of prioritizing medicines could aptly be described as having been inconsistent and contentious. As recent as during the 2015 parliamentary election debates, current prime minister Lars Løkke Rasmussen and then-candidate Helle Thorning Schmidt both stated during a debate that patients in the Danish healthcare system should be given access to all new medicines, no matter the cost (Andersen, 2015). However, simultaneously with these debates, the first drafts for a new medicine prioritization agency, what would become the Danish Medicines Council, were being created. The Danish Medicines Council was introduced on January 1st, 2017 with the mission of ensuring that new medicines in the hospital system are evaluated on the relationship between their efficacy and their cost. The Danish Medicines Council was introduced as a consequence of steadily rising costs of hospital medicines. In the ten years from 2007 to 2017, costs of sourcing medicines for the Danish public hospitals more than doubled at a growth of 110%, from approximately 4 billion to more almost 8.5 billion DKK. In the same period, the Danish GDP grew approximately 6% (EU-oplysningen, 2017). Thus, the growth in hospital medicines costs cannot be sustained at the current rates in the long term.

The unsustainable growth rates raise the question of how the costs of hospital medicines can be constrained in the long term. Policy makers are faced with the question of how to balance access to new medicines for patients with the burdens of the rising costs of new and existing medicines. However, these decisions cannot be made in isolation. One must also look at the effect of these decisions on the private pharmaceutical industry, which is responsible for investing in research and development of new medicines.

This paper aims to explore different methods of pricing medicines. A holistic approach is taken, considering payer affordability, patient access to medicines and the effects on private pharmaceutical research and development simultaneously.

2.1 Problem statement and thesis outline

The motivation for choosing this thesis topic comes from the topicality of the issue, as well as the importance of finding a solution to the unsustainable growth in the costs of hospital in the Danish public healthcare system. Thus, the following problem statement has been formulated:

From the perspective of payers, what is the most sustainable model for pricing hospital medicines in the Danish healthcare system?

To sufficiently answer the problem statement, it is broken down into four research questions. Combined, the answers to these four research questions aim to answer the problem statement. The research questions are:

1	SECTOR ANALYSIS	How are medicines introduced and priced in the Danish public healthcare system?
2	PROBLEM IDENTIFICATION	What are the main challenges in the Danish public healthcare system in pricing medicines, from the perspective of payers?
3	PRICING MODELS	What other medicine pricing models exist, and what are the benefits and challenges associated with them?
4	PROBLEM SOLVING	How can the challenges associated with pricing medicines in the Danish public healthcare be addressed?

The first research question investigates how medicines are introduced and priced in Denmark. An understanding of these processes is necessary in order to analyze potential challenges related to pricing medicines. A description of the processes involved in introducing a hospital medicine into the Danish public healthcare system is presented in Chapter 6.

The second research question looks at the main challenges in pricing medicines in the Danish public healthcare system. The challenges are identified based on interviews with stakeholders in the industry, as well as with this paper's own analysis of the potential issues with the processes described in Chapter 6. The main challenges are outlined in Chapter 7.

The third research question presents and analyzes the different types of medicine pricing models that are used in Denmark and selected, comparable European healthcare systems. The reason for the selection of the models that are analyzed is presented in Chapter 3. The medicine pricing models are analyzed for their benefits and challenges. The rationale behind this research question is to gather tools that may be used to solve the challenges that are identified in Chapter 7. The medicine pricing models are presented and analyzed in Chapters 8, 9, and 10.

The fourth and final research question aims to apply the selected medicine pricing models to solve the identified challenges. Thus, this research question combines the medicine pricing models that are presented in Chapters 8, 9, and 10 in order to solve the challenges identified in Chapter 7. The fourth research question is answered in Chapter 11.

Chapter 5 of this paper does not pertain to any specific research question in particular. Rather, it presents the topics of patents, price discrimination and parallel trade. Because these topics are by definition international, they are not directly part of the Danish healthcare system. Nonetheless, they greatly influence the effect of different pricing models.

2.2 Delimitation

This section covers the delimitations that are chosen for the scope of the paper. The delimitation covers the following aspects: First, the methods that are used to analyze the Danish public healthcare system in order to determine and regulate fair prices. Second, the geographic scope of the paper and its analyses. Third, the types of medicines that are included for analysis. Fourth, the temporal delimitation of the paper. Fifth, the scope of ethical considerations in the paper.

2.2.1 Methods to determine and regulate fair prices

Regulators face two distinct challenges when it comes to implementing policies on fair medicine prices. First, they must find a way to determine what constitutes a fair price. Second, they must implement policies that try to ensure that these prices are realized. When it comes to determining a fair price for a medicine, one may choose between any number of approaches. As outlined in the problem statement, this paper focuses on models of pricing. Thus, the choice of policy approaches that are analyzed in this paper are determined by the existing literature on models of pricing general goods, referred to in this paper as non-specific pricing models. These policies are used to both determine what level of prices can be considered fair, but also to regulate prices.

One could choose to utilize any number of policy approaches that could be expected to influence prices. For example, changing patent legislation, international trade laws, laws governing parallel trade of medicines in the European Union, and so on. However, this paper limits itself to policy recommendations that can be implemented within the existing international legal and political framework. It is hoped that such a delimitation increases the likelihood that the identified recommendations can realistically be implemented.

2.2.2 Geographic scope

This paper analyzes the different models of pricing medicines in the Danish healthcare system. It is argued that there is a significant amount of complexity inherent in the pricing of medicines in Denmark alone. For this reason, it is not considered feasible to analyze the many different medicine pricing systems that exist across multiple countries, as this would require taking into account the different political, economic and legal systems of every country. Instead, this paper focuses on a more in-depth analysis of the Danish healthcare system. An international context to the thesis topic is provided by incorporating analyses of the application of medicine pricing models in selected European countries.

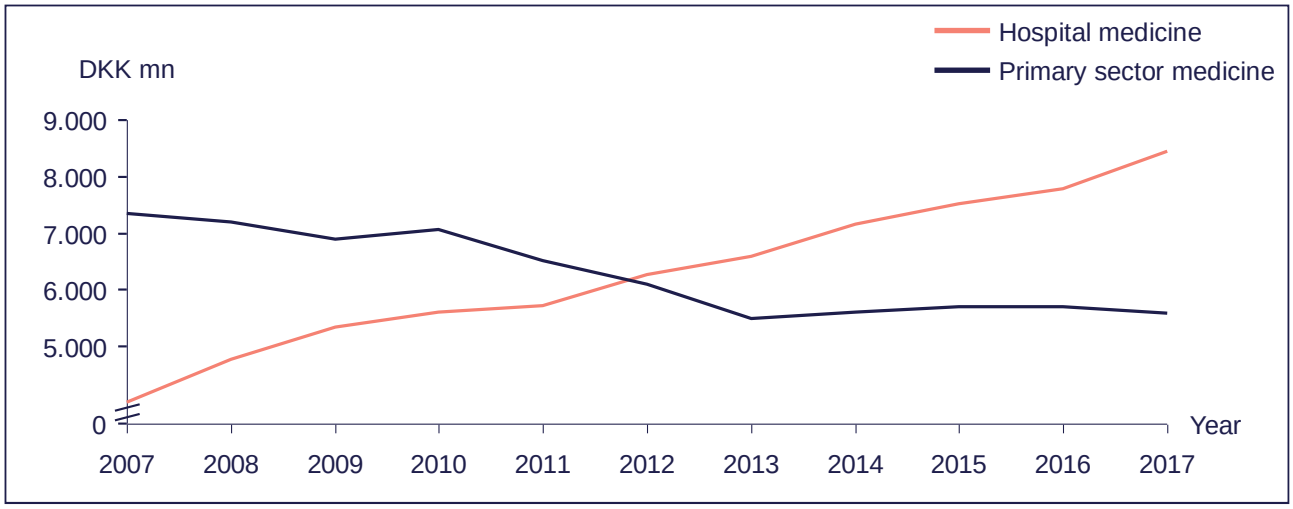
2.2.3 Types of medicines

There are two types of medicine that make up the total cost of medicines in the Danish public healthcare system. One type, which is at the core of this paper, is hospital medicines[1]. These include medicines that are sold to and administered in hospitals. The other type, which is not covered by this paper, is primary sector medicines[2]. These include medicines that are sold to patients at pharmacies

[1] Sometimes referred to as inpatient medicines in the literature
[2] Sometimes referred to as outpatient medicines in the literature

and which are taken at home by the patient. There are differences between hospital medicines and primary sector medicines in many areas, including the process of cost-effectiveness evaluation (and the evaluation metrics), their introduction into the healthcare system, existing price cap agreements, and more. This paper chooses to exclude the primary sector medicines from its scope. This is done for two reasons. First, the historical development in the cost of medicines is only challenging for hospital medicines. As depicted in Figure 2.1, the costs of sourcing medicines to the Danish hospital system has risen an average of 7.7%[3] per year over the last 10 years. In contrast, the costs of primary sector medicines (through reimbursement to medicines sold in pharmacies) has *declined* an average of 2.7%[3] per year in the same time period.

Figure 2.1: Medicine expenditures by sector



Source: figure by author based on Albinus (2018)

Thus, it is argued that there is not a significant challenge in terms of managing the costs of primary sector medicines. The second reason is that, because of the many differences between the ways the two types of medicines are priced, including primary sector medicines into the scope would add a significant amount of complexity to the paper. By limiting the scope to the hospital sector, it is possible to go into more depth with both description and analysis of the hospital sector.

2.2.4 Temporal delimitation

The topic of this thesis is rapidly evolving, especially given that the Danish Medicines Council has only been in existence slightly more than a year at the time of writing (Medicinrådet, n.d.). Due to time constraints, the research for this paper has been conducted over several months, alongside the rapid development of many important milestones, including discussions on the Danish Medicine

[3] Measured as the geometric mean, also referred to as compound annual growth rate ("CAGR") in some literature

Council's first disapproved medicine. Thus, certain developments may have been descoped from this paper due to them occurring after the research period. Nonetheless, this is considered an unavoidable challenge when writing about an issue that is so topical and rapidly evolving. Furthermore, a hard stop on including any new literature released after May 1st 2018 is enforced.

2.2.5 Ethical considerations

The topic of pricing medicines is highly controversial, as it necessarily deals with the topic of putting a monetary value on human health and wellbeing. Different theories of ethics could potentially be applied to support analyses of different pricing approaches. However, this paper only briefly touches upon the concepts of utilitarianism and economic notions of equity, and in these cases only as a supporting argument for or against the applicability of a pricing model. This delimitation serves to simplify the recommendations, as balancing the interests of payers, producers and patients in itself presents a significant challenge.

2.3 Definition of key concepts

This paper uses some concepts, which may be interpreted broadly, in a very specific manner. Thus, a definition of some of the key concepts applied in this paper is presented below.

Non-specific pricing model: Non-specific pricing models are defined in this paper as any theoretical model used by companies to determine what price to charge for a good or service. These models are not specifically aimed at pricing medicines, but are generic in nature.

Medicine pricing model: In the context of this paper, this term refers to any model of pricing used to determine the price of a medicine. These models may be used by the pharmaceutical companies to determine what price to charge, or it may be used by regulators to determine the amount of money they are willing to pay for a medicine.

Fair price: The concept of a fair price is, within economics, typically limited to study in the field of behavioral economics, and is highly based on subjective perceptions (Rotemberg, 2011). Besides issues of allocative inefficiencies (e.g. from imperfectly competitive markets or monopolies), prices are, in classic economics, generally not seen as "fair" or "unfair", they are simply the product of the competitive forces of supply and demand (Cabral, 2000). However, in the realm of medicines, ethical considerations may complicate the concept of demand. As noted by the World Health Organization (WHO, 2017) at the 2017 Fair Pricing Forum, "[…] *consumers may be prepared to pay whatever they can afford. A price that all patients can afford reflects the moral obligation to make medicines*

available to everyone who has a need". It is noteworthy that this discussion, while being especially topical now, has been ongoing for the last few decades. Spinello (1992) noted that "*beyond any doubt, instances of questionable and excessive drug prices abound*", using the example of azidothymide, which was priced at 6,500 USD per year. Even adjusting for inflation[4], this number pales in comparison to recent examples of medicine pricing, at 850 thousand USD (Kaltenboeck and Bach, 2018).

The necessity of medicinal prices to incentivize the research and development of new medicines is highlighted by the World Health Organization, defining a fair price as "one that is affordable for health systems and patients and that at the same time provides sufficient market incentive for industry to invest in innovation and the production of medicines" (WHO, n.d.). This argument is sometimes used by the pharmaceutical industry in a questionable manner, arguing that price increases of generic medicines may be used to fund future research, justifying large and immediate price increases by as much as 5,000% (Allhoff, 2015). In addition, the pharmaceutical has historically been highly profitable, with return on invested capital being higher than that of any other industry from 1995-2004 (Jiang and Koller, 2006).

In conclusion, while the concept of a fair price may be difficult to quantify, this paper aligns its definition of a fair price with that of the World Health Organization. Thus, a fair price is one that optimizes patient access, payer affordability, and incentives for continued investment in research and development by the private pharmaceutical industry. Achieving such a fair price is the goal of the sustainable pricing model that is sought after in this paper's problem statement.

Rationally containing costs: The concept of rationally containing costs is used in this paper to mean regulating or limiting excessive prices. Excessive prices are those that grossly exceed the concept of a fair price, as previously defined.

[4] 6,500 USD in 1992 has the same buying power as 11,792 USD in 2018 (Bureau of Labor Statistics, n.d.)

3 Literature review

This chapter describes the existing literature on medicine price regulation and medicine pricing models. Section 3.1 first reviews existing literature on the topic of regulating medicine prices. A gap in literature, that this paper seeks to fill, is identified. Furthermore, an overview of the main non-specific pricing models is presented, and their links to medicine pricing models are described. In subsections 3.2, 3.3 and 3.4, the theoretical foundations of the non-specific pricing models, and their analogous medicine pricing models, are presented. This is accompanied by an overview of the existing literature on the specific medicine pricing models.

3.1 Literature on medicine price regulation

Rising costs of medicines is a widely recognized challenge in the academic literature (Greene and Padula, 2017; Alexander et al., 2017; Acosta et al.; 2006; Kaltenboeck and Bach, 2018). Significant literature exists on the topic of managing the costs of medicines. Acosta et al. (2006) reviewed 18 studies covering the effect of introducing pricing policies and cost containment measures on the prices and costs of medicines. The review article mostly covers studies focusing on reference pricing (both internal and external), but note that additional pricing policies exist, including profit control. The authors found that reference pricing was generally an effective policy tool for reducing both prices and costs, and for shifting patients to lower-cost medicines (Ibid.).

In a more recent review, Alexander et al. (2017) reviewed 22 peer-reviewed articles addressing potential solutions for managing costs in the United States. Because this paper limits its focus to reviewing potential policy suggestions to the Danish public healthcare system, not all of the authors' identified solutions can be considered relevant for this paper. The review article classifies potential solutions into five broad categories: reviewing the patent system, incentivizing new drug development, altering pharmaceutical regulation, decreasing market demand, and developing alternative pricing policies. Given the delimitation of this paper, a specific interest is taken to the latter category. Ignoring the policy recommendations that are entirely specific to the US healthcare system, the pricing policy suggestions can be classified into four further sub-categories: value-based pricing, profit control, external reference pricing, and price caps (Ibid.). This paper argues that the former three of these sub-categories may be used to determine a fair price, whereas price caps are only useful for stabilizing prices once they are at a level that is assessed as appropriate (i.e., the level at which the price cap should be implemented must be determined by another method).

In a review of pharmaceutical regulation across 15 European countries, Panteli et al. (2016) found that most European countries had some degree of price regulation policies, with only a minority of countries allowing pharmaceutical companies to price freely. The authors identified three main pricing strategies that were employed across multiple European countries. These were external reference pricing, internal reference pricing, and value-based pricing (Ibid.). They also note the special case of profit control in the United Kingdom.

In another article, Carone, Schwierz and Xavier (2012) also analyzed cost-containment policies in medicines across the entire European Union. The authors identified three main methods that may be used to regulate prices: External reference pricing, internal reference pricing, and health-technology assessments based on cost-effectiveness criteria, essentially a form of value-based pricing.

Medicine pricing in the thirty member countries of the Organisation for Economic Co-operation and Development ("OECD") was covered in 2008 in a report by the OECD (OECD, 2008). They identified three main methods of pricing medicines: External reference pricing, internal reference pricing, and value-based pricing. Furthermore, they note that other medicine pricing methods include profit control and risk-sharing agreements (Ibid.). Similar to price caps, this paper argues that risk-sharing agreements by themselves do not allow one to put a price on a medicine; rather, they may be used as part of an agreement for a medicine whose price has already been established. Thus, it is not considered a direct medicine pricing model.

An overview of the identified review articles, their scope, and the main medicine pricing models which are identified as being relevant for this paper (based on the delimitations of this paper) is presented in Table 3.1.

Based on the presented literature, a gap in the literature is identified. Existing literature largely focuses on either of two approaches. The first approach consists of looking at a singular model of pricing medicines, either from a theoretical or simulated perspective, or applied to one or more healthcare systems. This focus typically presents detailed benefits and challenges of a singular pricing model, sometimes with empirical data on the implications of the model. The second focus is on cross-country comparisons of healthcare systems, which deconstructs the components of medicine pricing in multiple countries. This focus typically provides an overview of country-based differences but offers little in-depth analysis of the implications of the individual pricing models. Thus, this paper aims to fill the gap in literature by providing a comprehensive analysis of a single healthcare system, Denmark, looking at multiple pricing models. To solidify the relevance of this paper, it is noted that

there is a lack of up-to-date analyses on the Danish healthcare system, given the recent introduction of the Danish Medicines Council.

Table 3.1 Overview of review articles on medicine pricing models

Authors	Scope of study	Relevant medicine pricing models
Acosta et al. (2006)	Review of reference pricing and other pricing policies for medicines (18 studies included in review)	External reference pricing Internal reference pricing Profit control
Alexander et al. (2017)	Review of medicine cost-containment policies (22 studies included in review)	Value-based pricing Profit control External reference pricing
Panteli et al. (2016)	Review of pricing policies in 15 selected European countries	External reference pricing Internal reference pricing Value-based pricing Profit control
Carone, Schwierz and Xavier (2012)	Review of medicine cost-containment policies across the entire European Union (28 Member States)	External reference pricing Internal reference pricing Value-based pricing (Health technology assessments)
OECD (2008)	Medicine pricing policies across the OECD (30 member countries)	External reference pricing Internal reference pricing Value-based pricing Profit control

Source: table by authours (2018) based on chapter findings

In alignment with the problem statement, non-specific pricing models constitute a point of departure for the selection of medicine pricing models. Looking at pricing in this more generic context, Nagle, Hogan and Zale (2013) outline three primary approaches when it comes to pricing a product. The first approach, which is also the historically most common, involves basing the price of the product on the cost of production, with an added margin to ensure the company earns some profit. This approach is often referred to as cost-plus. The second approach is one based on pricing the product based on the value that the product delivers to the customer, often referred to as value-based pricing. The third approach is market-based and relies on pricing the product relative to competitors' products. The distinction between these three types of pricing approaches are in line with Hinterhuber (2004) and Liozu (2017).

This paper argues that for each of these three identified non-specific pricing models, there is an analogous medicine pricing model. As listed in Table 3.1, it is apparent that the existing literature identifies four main medicine pricing models: External reference pricing, internal reference pricing, value-based pricing, and profit control. Furthermore, there are two methods which do not in themselves constitute a medicine pricing model, but which may be used as part of a sourcing contract:

risk-sharing agreements and price caps. The non-specific pricing models, and their analogous medicine pricing models, are listed in Table 3.2.

Table 3.2 Comparison of non-specific pricing models and analogous medicine pricing models

Non-specific pricing model	Analogous medicine pricing model
Cost-plus	Profit control
Value-based	Value-based pricing, internal reference pricing
Market-based	External reference pricing

Source: table by authors (2018) based on chapter findings

The following parts 3.2, 3.3, and 3.4 go through the three non-specific pricing models, outlining the link between them and their equivalent medicine pricing models. Furthermore, the most significant literature on each medicine pricing model is presented.

3.2 Value-based

3.2.1 The link between value-based pricing in general and in medicines

The most obvious connection between a non-specific pricing model and the equivalent medicine pricing model is that of value-based pricing, as the method is directly comparable. Multiple studies suggest utilizing value-based pricing as an appropriate policy response to managing costs of very expensive medicines (Panteli et al., 2016; Porter, 2010; Kaltenboeck and Bach, 2018; Simoens, 2011; Jayadev and Stiglitz, 2009). Under value-based pricing, the price of a product (e.g. a medicine) is determined by the differentiation value that the product delivers to its consumers compared to the next-best competitive alternative (Nagle, Hogan and Zale, 2013). Thus, to set a price, a seller would begin with the price of what it expects the consumers to perceive as the next-best competitive alternative to its product, and then add or detract from this the differentiation value of its product (Dholakia, 2016). The differentiation value may be positive or negative, or a combination of both. In the case of medicines, there is likely to exist a current standard treatment. This is the comparator medicine that health technology appraisal bodies will typically compare the new medicine to. The differentiation value can take many forms. It may be more (less) effective at treating the disease, it may have fewer (more) or less serious (more serious) side effects, or it may be more (less) convenient or comfortable for the patient to take the medicine or have it administered to them, all of which would generate positive (negative) differentiation value. Thus, under value-based pricing, a maximum limit for the price that the pharmaceutical company would expect its customers (e.g. a single-payer public government) to be willing to pay for its medicine can be described by the following formula:

$$P_{n\_\max} = P_{comp} + V_D$$

where P_{n_max} is the maximum price of the new medicine, P_{comp} is the price of the comparator medicine, and V_D is the sum of positive and negative differentiation value, stemming from the relative to the comparator medicine.

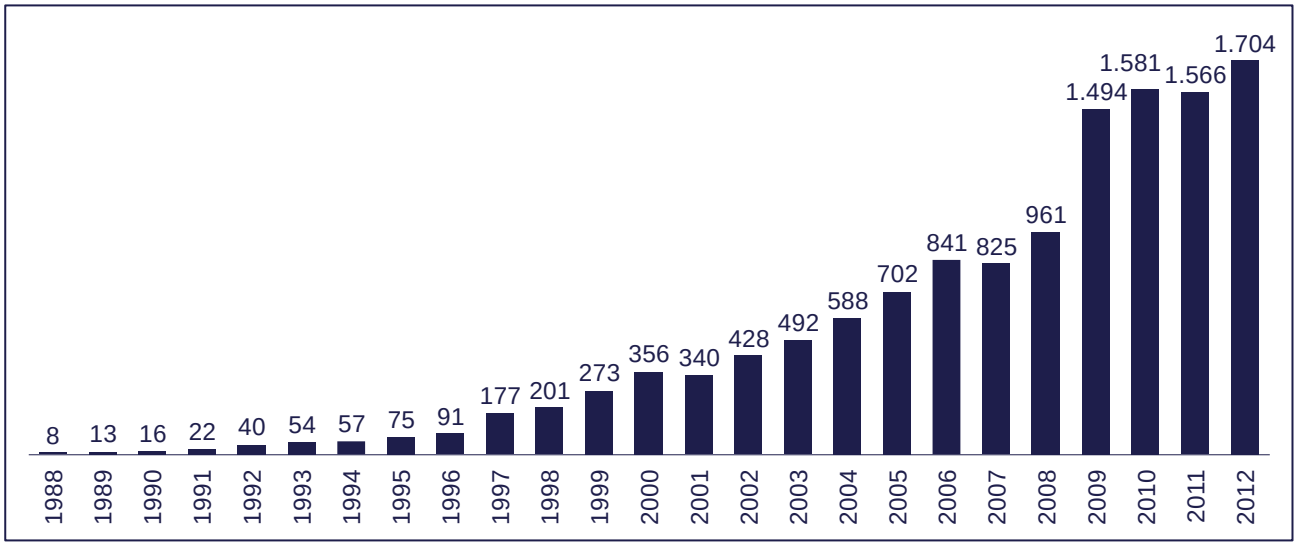
It is noted that multiple studies differentiate between internal reference pricing and value-based pricing (e.g. Alexander et al., 2017; Panteli et al., 2016). Internal reference pricing is defined by Panteli et al. (2016) as "[determining] pharmaceutical prices based on marketed equivalent or similar products within the country", and by Acosta et al. (2006) as "*using the price(s) of identical medicines (ATC 5 level) or similar medicines (ATC 4 level) or therapeutically equivalent treatments within a country to derive a benchmark or reference price for the purpose of setting or negotiating the price or reimbursement of medicines in a given country*". This paper does not agree with the need for such a distinction. Instead, it is argued that internal reference pricing is one specific application of value-based pricing. Using similar or identical medicines to benchmark prices is the exact same method that is applied under value-based pricing when determining the next-best competitive alternative. If the referenced medicine is identical (e.g. generic) or similar (in terms of efficacy and safety), then the differentiation value is simply zero. Thus, this paper does not make an explicit distinction between internal reference pricing and value-based pricing in from this point.

3.2.2 Literature on value-based pricing in medicine

The concept of basing the price of a medicine on its value has largely been centered around the concept of measuring cost-effectiveness using so-called quality-adjusted life years (QALY). The foundation of this approach was presented by Fanshel and Bush (1970). In their seminal paper, they develop an operational definition of health, "*based on one's ability to carry on the usual daily activities appropriate to social roles*". This theoretical foundation was further developed in a milestone paper by Weinstein and Stason (1977), where they first introduce the concept of quality-adjusted life years as a measure of the benefits of a medical intervention. The concept relies on quantifying the life years gained by the medicine, weighted by a quality factor ranging from 0 to 1, with 0 representing death and 1 representing perfect health. As the authors write, "*the underlying premise of cost-effectiveness analysis in health problems is that, for any given level of resources available, society (or the decision-making jurisdiction involved) wishes to maximize the total aggregate health benefits conferred*" (Ibid.).

The use of quality-adjusted life years in cost-utility analyses ("CUA") has been largely adopted into many health technology assessment bodies and reimbursement systems across the world. Wisløff et al. (2014) reviewed such analyses and found that the number of cost-utility analyses published every year had risen dramatically in the period 1988 to 2012. This rise is depicted in Figure 3.1. However, the widespread use of quality-adjusted life years has been met with some critique.

Figure 3.1: Number of CUA publications by publication year



Source: figure by authors based on Wisløff et al. (2014)

Puma and Lawlor (1990) presented critique of the utilitarian approach that is embodied in the use of quality-adjusted life years, noting that "using quality-adjusted life-years for health policy decisions is problematic and speculative". Furthermore, Pettitt et al. (2016) conducted an extensive review of existing literature on the limitations of using quality-adjusted life years in the evaluation of new medicines. The review studied 201 publications and classified the critique into three main categories: ethical considerations, methodological issues, and theoretical assumptions and context or disease specific considerations. However, they nonetheless note that "QALY is still regarded as the most rigorous methodological tool available and provides a robust framework to guide healthcare providers" (Ibid.). Furthermore, some scholars (e.g. Garrison et al., 2017) advocate for the use of more measures of value in cost-effectiveness analyses, going beyond standard measures such as quality-adjusted life years gained.

3.3 Cost-based

3.3.1 The link between cost-based pricing and profit control in medicines

Cost-plus pricing is a method of setting prices where the price of the product is determined by first looking at the costs of production, and then adding a margin to recoup these costs and provide some degree of profit for the firm (Nagle, Hogan and Zale, 2013). From a perspective of profit maximization, the shortcomings of this approach are especially clear in the case of pharmaceuticals. Because medicines generally have enormous fixed, sunk costs of development, but generally very small (in the case of small molecule drugs) marginal costs of production (Danzon and Towse, 2003), setting a price based on a cost-plus approach heavily depends on assumptions about the volumes of sales. If the sales are higher than expected, then the average cost is lower, and cost-plus pricing thus indicates that one should lower the price of the medicine. Vice versa, lower-than-expected sales will under cost-plus pricing suggest that prices be raised in a futile attempt to recoup the fixed costs. In both cases, the result of the approach is counter-productive if one aims to maximize profits for the firm. (Nagle, Hogan and Zale, 2013).

However, if one applies the same logic of the cost-plus pricing in setting the price of medicines, but looks at it from the perspective of payers, then one can understand the appeal as a policy tool. Developing a new medicine is enormously expensive, at an estimated cost of approximately 2.6 billion USD on average (about 16.2 billion DKK) (Alexander et al., 2017). However, once a product is marketed, it may become prove to be highly commercially successful and generate significant profits to the pharmaceutical company that developed it. In 2017 alone, the best-selling medicine in the world, adalimumab, marketed as Humira by AbbVie, generated more than 18 billion USD (Statista, n.d.), or about 112 billion DKK, in sales, many times the estimated average cost of developing a new medicine, at 2.6 billion USD (Alexander et al., 2017). From the perspective of payers, it may be of interest to limit the price of such a medicine, once the costs of R&D have been recovered to such an extent. If AbbVie had used cost-plus pricing, then the extremely high sales would have prompted significant price decreases. This is unlikely to happen, but in a single-payer healthcare system, the government may implement profit control, which limits the profits of the pharmaceutical company. Under such regulation, the outcome would be similar to that if the company were using cost-plus pricing. Thus, it is concluded that profit control policies to contain costs in medicine are analogous to a cost-plus pricing approach.

3.3.2 Literature on profit control in medicine

Rate-of-return regulation is a commonly-used tool to limit the allocative inefficiency of monopolists (Cabral, 2000). However, existing literature on profit controls within medicines mostly covers the profit controls in place in the UK, as it is a large market and one of the few to have implemented such a policy (Schulenburg, Vandoros and Kanavos, 2011). Profit control was introduced in the UK in 1957, and under the agreement, pharmaceutical companies may price branded medicines freely, but the profit cannot exceed the agreed limit (Łanda et al., 2009). If the pharmaceutical company's profits exceed this limit, then the company is obliged to either discount the medicine or return the excess proportion of profits (Ibid.). Schulenburg, Vandoros and Kanavos (2011) found that profit control appears to be effective in lowering prices of ACE inhibitors (a type of medicine for the treatment of elevated blood pressure), although they note the limitation of studying a single type of medicine. Sood et al. (2009) similarly found profit control to be an effective measure at reducing revenues for pharmaceutical companies, but note that other cost-containment measures appear to be similarly effective and that introducing additional policies do not appear to have an important effect on prices or costs.

3.4 Market-based

3.4.1 The link between market-based pricing and external reference pricing in medicines

Companies may also choose to set prices not based on either cost or economic value, but instead on the basis of its competitors' prices (Nagle, Hogan and Zale, 2013). Typically, this approach is used as a justification to lower prices to obtain sales goals. However, as demonstrated by Marn and Rosiello (1992), pricing discipline can be a powerful tool to improve profits, and the approach may prove fallible. Nonetheless, if one views market-based pricing as basing prices on other competitors' products, then the analogous situation from the perspective of the buyer is one where the buyer compares the price they are paying to what other buyers are paying. This is exactly the principle behind external reference pricing. Under external reference pricing, the payer (e.g. a government in a single-payer healthcare system) may request pharmaceutical companies to submit documentation for the prices charged in other countries, and then require the price in the local country to be similar, or even below, the average of the other selected countries. The choice of which countries to include in the basket of reference countries essentially determines the level of prices that the payer will accept. Similarly, the payer may require the prices to be either at the average, or below a certain percentile of the cost among the reference countries, also impacting the level of accepted prices.

3.4.2 Literature on external reference pricing

The literature on external reference pricing is quite extensive, especially covering the application of external reference pricing in European healthcare systems. In the short term, external reference pricing has mixed conclusions about the ability to lower prices. Brandt (2013) notes that in the short term, external reference pricing has led to large decreases in prices of up to 50%. Sood et al. (2009) reviewed 19 OECD countries that introduced elements of external reference pricing from 1992 to 2004 and found pharmaceutical companies' revenues dropped an average of 13.5% following the isolated introduction of external reference pricing. However, Rémuzat et al. (2015) reviewed 90 articles covering external reference pricing systems in Europe, and found mixed conclusions about the impact on prices, noting the significant and potentially adverse long-term effects of applying external reference pricing. Young, Soussi and Toumi (2017) provide a harsher critique of the external reference pricing model, calling the implications of it "perverse", due to the model leading to price convergence between high-income and low-income countries. This greatly reduces affordability in low-income countries. A similar worry is expressed in a report from Europe Economics (2013), and Espin, Rovira and Olry de Labry (2011). Furthermore, Persson and Jönsson (2015) demonstrate how external reference pricing incentivizes pharmaceutical companies to act in ways that are not welfare-maximizing. In addition, they use the case of abiraterone, marketed as Zytiga for the treatment of prostate cancer, to show how easy it is to circumvent the mechanisms of lowering prices by using external reference pricing. They conclude by predicting the end of external reference pricing for these reasons.

4 Research methodology

One may categorize the way research is conducted on a basis of multiple characteristics, including the research philosophy to which it subscribes, the scientific approach that is employed, and the choice of research methodology (Sauders, Lewis and Thornhill, 2012). This section describes the research philosophy that guides the approach that this paper takes towards collection, analysis and utilization of data. Furthermore, the specific research methodology of this paper is presented, covering the specific details of how data is gathered.

4.1 Scientific approach and research philosophy

The choice of scientific approach and research philosophy that is applied is strictly bounded by the problem statement and underlying research questions. This paper applies a largely interpretivist philosophy to its research, noting in line with Saunders, Lewis and Thornhill (2012) that the interconnected network of pharmaceutical companies, policymakers, patients, and other industry stakeholders, is far too complex to be described by 'laws' in the same way as natural sciences under a positivist philosophy. Saunders, Lewis and Thornhill (2012) note that the interpretivist approach emphasizes the subjective interpretation of the researcher. Thus, under an interpretivist approach, the researcher cannot be said to be independent of the subject being researched. The semi-structured nature of the research in this paper embodies this subjectivity, as the researchers will unavoidably have an integral part in forming the research while it is being conducted. Beyond the collection of data, the interpretation of the important topics in the data is also highly subjective.

The chosen scientific approach is largely determined by the perceived nature of the theories and observation, and is typically bounded to either the inductivism or deductivism (Chalmers, 2013). Chalmers (Ibid.) notes that while inductivism cannot reasonably lead to any inference of a truthful description of reality in itself, research performed using an inductivist approach guides the formulation of theories that may be tested using a deductivist (falsificationist) approach. Thus, while this exploratory research of the Danish public healthcare system does not allow one to confidently generalize across other healthcare systems, it may guide the development of theories to be tested in further research, as it helps form the basis for the formulation of general theories.

4.2 Research methods

As described in the literature review in Chapter 3, the existing literature on the chosen thesis topic is quite compartmentalized, with several discrete topics being well-described. However, answering the

identified problem statement and underlying research questions requires a cohesive connection between the many different topics, including pricing theory, economics, and models of health technology appraisal. It is hoped that this paper contributes to the existing literature by bridging the gap between these disciplines, and to do so, a rather explorative approach to research is employed. This approach combines both a significant amount secondary research, as well as primary research conducted by the authors of this paper. It is argued that the thesis topic has not been adequately explored from a cross-disciplinary approach, and thus that the collection, categorization and application of existing, secondary research by itself constitutes a valuable contribution to the literature, in line with Rugg and Petre (2006). Explicitly, this paper aims to achieve this by reviewing how the benefits and challenges of different medicine pricing models may indicate the use of the models under certain circumstances, and where it may be advisable to use other measures, given the unique challenges of the Danish public healthcare system. However, this is supplemented by primary research conducted by the authors of this paper, which is described in greater detail in Part 4.2.1. This primary research is mostly aimed at determining the real-world application of the theoretical models that are assessed, and the hope is that this increases the feasibility of implementing the proposed final policy recommendations.

4.2.1 Interviews

Primary data was collected by way of interviews with industry stakeholders from the pharmaceutical industry, the Danish government, as well as patient representatives and subject matter experts, mostly professors. Thus, the interviewees represent all three types of stakeholders whose interests this paper aims to balance: the payers, who aim to minimize costs of sourcing medicines while also ensuring that the private pharmaceutical industry continues to develop new, effective medicines; the patients, who seek access to the newest and most innovative medicines; and the pharmaceutical companies, who seek to profit from the development, production and sales of new and generic medicines. A full list of the interviewees is found in Appendix B. A breakdown of the categories of stakeholders shows that out of a total of twenty interviewees, eleven may be classified as subject matter experts. This category consists mostly of university professors in Denmark, Germany and the United States, but also includes doctors (without any medicine sourcing responsibilities) and consultants working with, but who are not employed by, the pharmaceutical industry. Five may be classified as representing the payers of medicine in the Danish public healthcare system, being either directly involved in the assessment and sourcing of medicines, or indirectly by setting the policy frameworks that govern the related processes. Three interviewees represent the pharmaceutical industry, and one interviewee

represents the interests of patients in the Danish public healthcare system. Whiting (2008) notes the importance of selecting appropriate interviewees, based on their knowledge about the topic, their ability and availability to convey this information, and the preexisting relationship with them. Whiting (Ibid.) furthermore notes the risk of preexisting relationships affecting the nature of the interview. The interviewees in this paper were selected based on their expertise within medicine, the pharmaceutical industry, public government, health technology assessment and other topics which are directly related to the thesis topic. It is noted that there were no significant preexisting relationships between the authors of this paper and the interviewees beyond being connected through extended professional networks. Furthermore, no compensation was provided to interviewees for participating.

Due to the interest in interviewing a broad selection of stakeholders, but also being able to compare the answers across different respondents, it was decided to conduct the interviews in a semi-structured manner. The semi-structured interview is the most commonly used interviewing format in qualitative research, and it is often the only method of data collection in these types of qualitative projects (DiCocco-Bloom & Crabtree, 2006). The semi-structured interview format revolves around a set of predetermined questions listed in an interview guide. However, unlike structured interviews, the format does not necessitate more or less complete adherence to the listed questions in the interview guide (Saunders, Lewis and Thornhill, 2012). Furthermore, the questions tend to be more open-ended, which is ideal for this paper's topic, as balancing the different benefits and challenges of various aspects of pricing models may prove challenging and therefore require flexibility with regards to the route of discussion in the interview. This need for flexibility is exacerbated by the fact that the selected interviewees intentionally have very different backgrounds and fields of expertise. The choice of the semi-structured interview allows the researchers to focus on the topics where the interviewee has the most expertise and experience, ensuring more valuable contributions to the research.

The conducted interviews lasted between half an hour to approximately an hour and a half, with most lasting around five quarters. This is in line with typical lengths of this format of interviews (Jamshed, 2014). The interview guide, which the interviews were based upon, consisted of three main topics. First, interviewees were asked about their perceptions of benefits and challenges associated with different pricing models. Second, a specific topic of real-world evidence was brought up, asking interviewees about their perceptions of the feasibility of using this type of data to support pricing models. Finally, a topic of the Danish public healthcare system was addressed. For interview participants with non-Danish backgrounds, this section was modified this section to fit the local

expertise of the interviewee. This was the case for one interviewee in Germany, one in the United Kingdom, one in Sweden, and one in the United States. The time spent on each category was also tailored to the expertise of the individual interviewee, while remaining somewhat bound by the overall interview guide. For an example of a generic version of the interview guide used, please see Appendix C.

5 International considerations in pricing medicines

This chapter aims to provide a brief understanding of the international context of pricing medicines, with a focus on the price discrimination across markets and parallel trade. First, an argument for the necessity of patents in the pharmaceutical industry is presented. Then, a model of how producers of patent-protected medicines can be expected to use price discrimination across markets is derived, based on their monopoly power. Furthermore, the ability to perform price discrimination is considered, given the existence of the European Single Market. The chapter concludes with an analysis of how the legal framework of the European Union affects medicine affordability, the access to medicines, and innovation of new medicines.

5.1 The role of patents in the pharmaceutical industry

Pricing of medicines is inherently different from pricing of many other goods. Putting a price on what is essentially a person's life or quality of life remains extremely controversial, even taboo (Scanell, 2015). Furthermore, if one looks broadly at available medicines, there does not seem to be any correlation between the medical importance of a drug and its prices. Antibiotics, which are essential to any healthcare system, are abundant and inexpensive, while new medicines to treat cancer, with only marginal benefits, may be priced in the hundreds of thousands of Danish kroner per treatment (Ibid.). The lack of correlation between the price and the importance of the medicine is mainly due to the legal monopoly that is granted to innovator pharmaceutical companies through patents. It is widely acknowledged that patents are necessary to ensure sustained incentives for companies to innovate, especially in industries with large sunk costs of development, such as in the case of pharmaceuticals. Indeed, patents for pharmaceutical companies is a requirement for member states of the World Trade Organization (Danzon and Towse, 2003). If patents for innovative medicines did not exist, pharmaceutical companies would quickly face competition from generic producers after introducing a new medicine, pushing prices of medicines towards the marginal cost of production, leaving the innovator company unable to recoup the extensive costs of R&D, which are estimated at approximately 2.7 billion USD (DiMasi, Grabowski and Hansen, 2016) for the average new medicine. Thus, in the absence of patent protection, continued R&D investment would be unsustainable, and one would expect pharmaceutical companies to refrain from investing in further research and development, leading to a lack of new medicines being developed (Langinier and Moschini, 2002). The method of patent protection is in economic theory denoted as a second-best efficient outcome,

as it allows for the development of medicines that, without a patent system, would not have been developed. (Danzon and Towse, 2003; Langinier and Moschini, 2002).

5.2 International models of monopolist pricing in medicines

This section introduces two theories of how monopolists (e.g. a pharmaceutical company with a patent-protected medicine) are expected to price across international markets. An argument is presented that price discrimination across markets may in fact lead to profit maximization for the producer, maximum patient access to medicines (in low-income countries) and potentially lower prices of medicines for high-income countries

5.2.1 Monopolistic price discrimination

Given the necessity of having an effective patent system to incentivize the development of new medicines, economic and industrial organizational theory provides insight into the type of pricing behavior one would expect from pharmaceutical companies that have been granted such patents. Because the patent grants the pharmaceutical company temporary, legal monopoly through protection from competition, one can assume the company to set its price similarly to how a monopolist would. As a monopolist controls both the quantity supplied and the price of the product, it maximizes profits in a given market by choosing the quantity supplied that leads to the price where the marginal revenue is equal to the marginal cost (Cabral, 2000). If the price elasticity of demand is defined as:

$$\varepsilon = \frac{dD}{dp}\frac{p}{q}$$

where ε is the price elasticity of demand, D the demand as a function of price p, and q is the quantity demanded, then it follows that the monopolist sets a markup over marginal cost MC at the following level to optimize profits (Ibid.):

$$\frac{p - MC}{p} = \frac{1}{\varepsilon}$$

Thus, it is found that the monopolist will choose to set a price that is inversely proportional to the price elasticity of demand of the market. The implications of this will be covered in Part 5.2.2, after additional theory has been introduced.

Looking more specifically at the topic of medicine development, this paper follows Danzon and Towse (2003) and notes that two requirements must be met before the development of new medicines, and the introduction into a market, is sustainable over time. First, the price *p* in every served market *j* should be equal to or higher than the marginal cost of production in that market *j*, denoted as:

$$p_j \geq MC_j$$

Second, the prices charged for the medicine must be, in aggregate over all markets, sufficiently larger than the marginal cost of production *MC* for each market *j* so as to at least cover the costs *F* associated with developing a new medicine. The total costs of developing a new medicine includes a normal, risk-adjusted return on the invested capital, to accommodate the inherent risks associated with developing medicines. This is denoted as:

$$\sum (p_j - MC_j) \geq F$$

Note that there is no requirement that all markets should be served at the same markup. Recall that monopolists will maximize profits by setting the markup over marginal cost that is inversely proportional to the price elasticity of demand for the particular market. If markets differ in their price elasticity of demand, and the pharmaceutical company is able to price discriminate across markets, then it follows that the profit maximizing price will vary across different markets, in inverse proportion to the individual market's price elasticity of demand.

5.2.2 Ramsey optimal pricing

Another model for determining a monopolist's prices is Ramsey optimal pricing ("ROP"), which is fundamentally similar to the general model of monopolist pricing, but which includes a potential limit to profits. The model was first proposed by Ramsey (1927) in his foundational paper on taxes, but was extended by Baumal and Bradford (1970) and has since been used extensively in modeling pricing of public utilities for the purpose of welfare maximization (Schweitzer and Comanor, 2011). However, ROP may also be used in the case of pricing medicines if the pharmaceutical company has been granted a patent and constitutes a monopolist. Similar to public utilities, pharmaceutical companies have large fixed and sunk costs of developing new medicines, and low or negligible marginal costs to serve additional customers (Danzon and Towse, 2003). Thus, one may apply Ramsey optimal pricing to maximize total welfare for medicines. Following Danzon and Towse (2003), it is noted that the price differentials across markets are determined so as to maximize welfare.

This is subject to a requirement that the producer earns a target level of profit, which is typically a normal, risk-adjusted return on invested capital. The optimal price in a given market is determined by:

$$\frac{p - MC}{p} = \frac{D}{\varepsilon}$$

where *D* is the proportionality term that is applied to ensure the required level of profit for the producer is met. As a result, if one assumes marginal costs are identical across markets, then the only driver for price differentials across markets is the price elasticity of demand of the served market. The interpretation of the result is highly intuitive. Pharmaceutical companies are thus expected to charge a higher markup over marginal costs for markets with a lower price elasticity of demand, and a lower markup in markets with higher price elasticity of demand. Compared to a monopolist's profit-maximizing price, it is noteworthy that the Ramsey optimal price, which aims to maximize total welfare, not profit, is remarkably similar in its predicted price differentials across markets. The difference between the two models lies in the proportionality term in the ROP model, which is simply unity under standard profit maximizing models for monopolists. The interpretation is that, if one assumes marginal costs to be identical across market, absolute price levels predicted by the two models may differ, but relative prices between markets will be identical. As Danzon and Towse (2003) note, the similarity of the results from the two models is fortuitous, as a self-interested pharmaceutical company with a patent protection will set prices that simultaneously optimizes profits, but also provides the second-best efficient outcome and optimizes total welfare.

Danzon and Towse (2003) assume that low-income countries will display higher levels of price elasticity of demand, and therefore argue that Ramsey optimal pricing represents an equitable outcome. However, this notion is met with criticism from Schweitzer and Comanor (2011) who argue that essential medicines would, under Ramsey optimal pricing, be priced higher than less essential medicines (as the elasticity of demand would be lower for life-saving, critical medicines). Taking this argument further, they utilize the example of antiretroviral medicines. They argue that the need and, by extension under Ramsey optimal pricing, the price, for these medicines would be higher in low-income countries plagued by HIV, compared to high-income countries where the disease presents less of a public health burden. A similar critique was put forth by Jack and Lanjouw (2005), noting

that "[ROP] prescribes higher prices in countries with greater need for drugs", concluding that this is difficult to align with standard notions of equity[5].

5.2.3 Peak load pricing model

Schweitzer & Comanor (2011) present an alternative method of pricing that, they argue, is more equitable than the results of Ramsey optimal pricing. The model was, like Ramsey optimal pricing, developed for pricing utilities. Similar to Ramsey optimal pricing, its focus is on optimizing welfare (consumer and producer surplus), rather than simply maximizing profits for the producer. Applying the model to the pharmaceutical industry, the basic principle of the model is that the fixed cost of developing a medicine must be covered by the primary markets (high-income countries), but secondary markets (lower-income countries) need not contribute to this. This pricing method involves differentiating price across markets by allocating different cost sources depending on the wealth of the country. Thus, developing economies are only charged a price that reflects the costs of production, at or slightly above the marginal costs of producing the medicine.

5.2.4 Comparison of international medicine pricing models

As mentioned, the primary difference between the general monopolist pricing model and the Ramsey optimal pricing model is that under Ramsey optimal pricing, a proportionality term that allows for different profit margins is introduced. Thus, a pharmaceutical company applying Ramsey optimal pricing may price at a certain markup over marginal costs that produces a specific return on invested capital, whereas under the general monopolist pricing model, profits are simply maximized. Nonetheless, the two models both rely on price elasticity of demand to set prices, and thus the relative prices between markets will be identical under the two models.

The distinctive feature of the peak load pricing model is that it directly equates the price of the medicine in a country to that country's level of wealth, rather than relying on price elasticity of demand. Thus, the equitable outcome of the model becomes more explicit than in the case of Ramsey optimal pricing. Under general monopolist pricing, and Ramsey optimal pricing, one must assume that there is a direct relationship between the wealth of the country and its price elasticity of demand for the model's results to be considered equitable.

One importing notion to consider under all three models is that price differentials across countries does not constitute cost-shifting, i.e. that high-income countries are overpaying due to low-income

[5] In the context of this paper, equity is defined as the equal access to medicines despite wealth differences

countries underpaying for medicines. If markets are separate, the firm is rationally expected to set prices independently of other markets. Noting that the costs of developing a medicine are fixed and generally not variable as to the number of countries that it is marketed to, as long as low-income countries pay anything more than the marginal cost of production, their contribution allows for lower prices in high-income countries (Danzon and Towse, 2003). Thus, if price discrimination across markets is allowed, the prices in high-income countries may actually be lower than if such price discrimination is not permitted.

Thus, this paper concludes that price differentials and price discrimination by pharmaceutical companies across markets can improve access to medicines internationally, maximize profits to the firm (incentivizing further innovation), and improve affordability of the medicine. These goals are in direct alignment with the notion of a fair price that is used by this paper.

5.2.5 Empirical evidence on international medicine prices

One notion that is common across the three presented international models of medicine pricing is that the price should vary across markets, either in accordance to the price elasticity of demand or the wealth of the individual country. But are price differences across markets actually observed? Empirically, several studies have indeed found a significant correlation between a country's GDP and the country's medicine prices. Schut and Bergeijk (1986) found, based on 1975 data, that a 10% per capita income increase resulted in an average increase of medicine prices of 8%. Schweitzer & Comanor (2011) found that middle-income countries had approximately 15% lower prices for medicines that were still under patent protection, and approximately 22% lower prices for generics, compared to industrialized countries (excluding the United States).

The reason for Schweitzer and Comanor's (2011) exclusion of the United States is that they have extraordinarily high medicine prices. Table 5.1 shows the medicine price indices in the US across three groups of medicines, with the medicine prices in industrialized countries set as 100.

Table 5.1 Index of medicine prices across country groups and medicine categories

	Patented medicines	Off-patent medicines	WHO essential drug
United States	267.4	123.6	694.4
Other industrialized countries	100.0	100.0	100.0
Middle-income countries	85.6	77.6	91.7
Developing countries	44.4	44.5	20.1

Source: table by author based on Schweitzer and Comanor (2011)

Schweitzer and Comanor (2011) found the prices of medicines in the United States to be approximately 2.7 times, 1.2 times, and 6.9 times the prices in other industrialized countries for patented medicines, off-patent medicines and WHO essential drugs, respectively. These price differentials greatly exceed the differences in wealth between the United States and other industrialized countries, and it prompts the question of whether these other countries are essentially "free-riding" on the high prices paid by the patients in the United States. This notion was also put forth by Dana Goldman, Director of the University of Southern California's Schaeffer Center for Health Policy and Economics (Goldman, pers. comm., April 12th, 2018). He stated that most European healthcare systems pay so relatively low prices for medicines that, if the United States were to pay similar prices, research and development by pharmaceutical companies would drop significantly or even stop entirely. The President of the United States, Donald Trump, announced a similar critique, accusing foreign countries of "freeloading" on pharmaceutical research conducted in the United States (Jopson and Crow, 2018). If such plans come to fruition, then it may be expected that prices in European countries, including Denmark, would have to rise in order to sustain current levels of innovation. If this happens, the need for the Danish policymakers to be able to determine and set fair prices would be greater than it is today, further heightening the relevance of this paper.

5.3 EU, free movements of good and parallel import

This section begins with an introduction to the European Single Market and its importance to the European Union, described in Part 5.3.1. In Part 5.3.2, the impact of parallel trade on medicine availability, affordability, and innovation is discussed.

5.3.1 The European Union and the European Single Market

The free movement of people, goods and services across European borders is a founding principle of the modern-day European Union (European Union, n.d.). The European Single Market is the trade agreement that guarantees free movement of goods across its member states, by eliminating customs, duties, tariffs and other trade restrictions internally. The European Single Market's member states are the same that comprise the European Economic Area ("EEA"), which are the 28 Member States of the European Union, as well as Iceland, Liechtenstein, Switzerland (through bilateral agreements) and Norway (UK Government, n.d.). In the context of this topic, the free movement of goods across the European Single Market has the implication that medicines sold in one EEA country may be traded and resold in any other member country (Danzon and Towse, 2003). This stands in contrast to other free-trade agreements, such as the North American Free Trade Agreement ("NAFTA"), which does not allow parallel trade of medicines (Ibid.).

5.3.2 The effect of parallel trade on price discrimination in the European Union

Section 5.2 describes how international models of medicine pricing all employ price discrimination across international markets. Furthermore, it is found that price discrimination may lead to greater patient access to medicines in low-income countries, greater profits for pharmaceutical companies (incentivizing further innovation) and even greater affordability of medicines for high-income countries. However, the free movement of goods across borders in the EEA may be a barrier to the degree of price discrimination that is possible for pharmaceutical companies to perform. Large differences in prices across markets attract actors that seek economic rents from arbitrage by purchasing in low-cost countries, transporting the product to high-cost countries, and reselling the product there at a profit.

The existence of parallel imports causes prices to converge at least partially across markets, as parallel importers underbid the manufacturer's local prices Ganslandt & Maskus (2004). This, in return, forces the manufacturer to lower prices in the local market, if they wish to remain competitive with parallel importers, converging towards similar prices across markets. The effects of this convergence can potentially be very dramatic. A study by Glynn (2009) found that a theoretical, perfect convergence of prices in the European Union of a patented medicine would significantly reduce affordable access to medicines in many low-income Member States of the European Union, as the pharmaceutical company will be disincentivized to market the medicine in countries with lower GDP at a proportionally low price. The author concludes that for this reason, "*the best option from the*

point of view of health care policy would be to prohibit the repackaging of medicines and require traceability throughout the supply chain" (Glynn, ibid.).

In practice, the data suggest that a majority of the economic rents of parallel importing medicines are earned by the parallel importers themselves, rather than through savings to governments. Ganslandt & Maskus (2004) found that approximately three fourths of the rents earned from parallel importing medicines were earned by the importers. Bart (2008) notes that the European Commission had similar concerns in a 1998 communication, stating that "unless parallel trade can operate dynamically on prices, it creates inefficiencies because most, but not all, of the financial benefits accrue to the parallel trader rather the health care system or patient". However, the Commission also noted the importance of the role of parallel trade in market integration and thereby in achieving the realization of the European Single Market (Ibid.).

There are additional challenges associated with parallel trade in the case of medicines. Beyond the indirect availability effect through converging prices (as pharmaceutical companies neglect to market their medicines in certain low-income countries at an appropriate price level), there is the direct availability challenge as medicine reserves intended for sale in the local, low-price country are exported by companies that sell to high-price countries. If the pharmaceutical company observes that medicines sold to a certain low-price country are often used to compete with their medicine in higher-price countries, the pharmaceutical company may not wish to restock the exported medicines or may even suspend delivering the medicine entirely. This leaves the governments of the low-price countries unable to source or afford the medicines, potentially causing serious public health issues (Bochenek et al., 2018). Based on interviews with Dorthe Søndergaard of the Danish Ministry of Health in Denmark, it is understand that this phenomenon is causing significant frustration among low-income countries in the European Union (Søndergaard, pers. comm., March 7th, 2018). There are other significant challenges rising from parallel importing medicines. Glynn (2009) estimates that risks stemming from incorrect relabeling, more inefficient product recalls (because parallel importers add their own serial numbers to relabeled products), and an increased risk of counterfeit products as reducing the value of the parallel imported medicines by approximately 10%, noting that parallel importing brings no benefits to patient safety.

5.4 Chapter sub-conclusion

This paper draws three main conclusions from this chapter. First, while monopolistic pricing is usually associated with allocative inefficiencies, international price differentials under a monopoly

may in fact be aligned with the notion of fair prices that is employed by this paper. Models of welfare pricing aimed at maximization provide similar results those that focus on profit maximization alone. Thus, international price discrimination may lead to greater patient access, larger profits for pharmaceutical companies (thereby incentivizing continued research and development), and greater affordability of medicines in both low- and high-income countries.

Second, it is noted that the excessive price premium on medicines that is currently paid by patients in the United States may not be sustainable. Industrialized countries, including many European countries, may expect to see continued rises on the prices of medicines in order to sustain current levels of innovation.

Finally, it is noted that the European Single Market and its allowance of parallel trade of medicines diminishes the ability for pharmaceutical companies to perform price discrimination. This, in turn, adversely affects access to medicines in low-income countries, the profits of pharmaceutical companies, and even potentially raises prices in high-income countries. Beyond this, parallel trade also introduces patient safety concerns, while the evidence for the benefits of parallel trade remains doubtful.

From an isolated perspective, this chapter's conclusions may not directly affect the pricing of medicines in Denmark. However, given the interconnectedness of pricing schemes in Europe and the rest of the world (Panteli et al., 2016; OECD, 2008), one should refrain from looking at Denmark in isolation. If US medicine price levels fall, Denmark will be impacted, either by being forced to pay more for medicines, or through reduced innovation at a global scale. Furthermore, the findings of this chapter affect the viability of external reference pricing as a pricing mechanism, as shall be demonstrated in Chapter 10.

6 Introducing and pricing new hospital medicines in Denmark

This chapter describes the processes involved in introducing and pricing a new hospital medicine in Denmark. Section 6.1 provides a description of how new medicines are granted marketing authorizations, as well as the process of introducing a new hospital medicine into the Danish public healthcare system. Section 6.2 provides a description of the price cap agreement that is in place for most hospital medicines.

6.1 How new medicines are introduced and priced

6.1.1 Regulatory approval

This section very briefly introduces the required steps for a pharmaceutical company to receive a marketing authorization for a new medicine. Medicines cannot be sold in any European Union Member State, including Denmark, without authorization to be marketed (Panteli, 2016). Thus, a key step for before any pricing decisions can be made, is to receive marketing authorization. A pharmaceutical company may choose to apply either through the centralized procedure, applying for marketing authorization for all countries in the European Economic Area ("EEA") simultaneously, or directly through one or more of the individual countries' competent authorities (Ibid.). Because the most medicines are assessed through the centralized procedure, this paper limits this description to centralized procedure.

The Committee for Medicinal Products for Human Use ("CHMP") is responsible for evaluating medicines under the European Medicines Agency. The pharmaceutical company submits a marketing authorization application ("MAA") through a standardized procedure known as the electronic common technical document ("eCTD") (EMA, n.d.). The CHMP assesses the MAA, and provides a positive or negative opinion on whether the medicine should be allowed to be sold in the EEA. It is noteworthy that while the CHMP does require that the drug displays efficacy in treating the disease, efficacy is not the main criterion for receiving marketing authorization (Panteli, 2016). Typically, a limited proof of efficacy demonstrated through comparison against a placebo (rather than the current standard treatment) from a small sample size is sufficient, as long as the pharmaceutical company can provide significant evidence that the drug is safe (Ibid.). Furthermore, there are no cost-effectiveness analyses taken into consideration as part of the MAA. Thus, one cannot consider a positive opinion from the CHMP as a guarantee that the medicine will be cost-effective compared to existing treatments. If the CHMP provides a positive opinion, the European Commission ("EC") will decide on whether to allow the medicine to be sold. The EC almost always follows the opinion of the CHMP,

with rare exceptions (EMA, n.d.). Once the EC approves the medicine, it may be marketed in the entire EEA.

An overview of the process of how a pharmaceutical company applies for an MAA is presented in Appendix A. This Appendix also presents the processes that are related to evaluating and pricing the medicine in the Danish public healthcare system, which is reviewed in Section 6.1.2.

6.1.2 Introducing a new hospital medicine

While the pharmaceutical company is still having its medicine evaluated by the EMA, the company may simultaneously begin the process of applying to have its medicine introduced into the Danish public healthcare system. This section provides a description of the process of applying for a new medicine introduced as standard treatment in the Danish hospitals.

There are two main organizations that the pharmaceutical company will interact with in the introduction and pricing process: the *Danish Medicines Council* ("DMC", "Medicinrådet" in Danish) and *Amgros*. The DMC is a health technology appraisal organization, responsible for developing an assessment of the clinical impact of medicines for hospital use. Furthermore, the DMC works to ensure that new and existing medicines are used homogenously across different regions and hospitals. Its role as a health technology appraisal organization is of critical importance for the pricing and sourcing of hospital medicines, as the DMC's assessment of clinical value is used as a basis for price negotiations (Medicinrådet, 2017). These negotiations are handled exclusively by Amgros. Amgros is a political partnership organization owned wholly by the Danish Regions whose purpose is to consolidate sourcing efforts for hospital medicines used in the Danish public healthcare system (Amgros, n.d.). Amgros negotiates prices with pharmaceutical companies, ensures stability of delivery and makes the medicine available for public Danish hospitals. Amgros ensured delivery and sourcing of approximately 99% of hospital medicines in Denmark in 2017, at a total price of approximately 8.4 billion DKK (Amgros, n.d.). This is spread across approximately 3,000 different medicinal products. However, the cost distribution is highly skewed, with just the top 100 medicines accounting for approximately 80% of the total cost of all hospital medicines, based on interviews with Flemming Sonne, the CEO of Amgros (Sonne, pers. comm., Feb. 2, 2018).

A simplified overview of the process of introducing a medicine into the Danish public healthcare system can be found in Appendix A. The pharmaceutical company may begin the process of having

its medicine introduced into the Danish public healthcare system before it has been granted a marketing authorization by the EMA. First, the pharmaceutical company may contact both the DMC and Amgros to book preliminary meetings no earlier than 22 weeks before the expected date of approval by the European Commission ("Day 0").

After meetings with the DMC and Amgros, the pharmaceutical company begins developing a preliminary application to submit to the DMC. Based on the preliminary application that is submitted, the DMC develops a protocol. This protocol is used as both a basis for the pharmaceutical company's final application. The protocol includes descriptions of the clinical questions, with detailed PICO (patients, intervention, comparison and outcome) descriptions.

Once the pharmaceutical company receives the protocol from the DMC, the company begins preparing for the final application based on the content of the protocol. The final application contains three parts: basic information about the medicine and indication, which is submitted to both the DMC and Amgros; clinical evidence, which is submitted to the DMC; and a cost analysis section, which is submitted to Amgros. The DMC begins the processing of the application and analyzes the clinical evidence supporting the application. The DMC evaluates the absolute and relative added clinical value of the medicine against its relevant comparator treatment. The DMC looks at the efficacy and safety profile of the medicine, as well as the quality of the data that makes up the evidence for these. Based on this, the DMC categorizes the medicine into one of six categories, representing different levels or classifications of the added clinical value. These categories are listed in Table 6.1. Positive added clinical value is separated into three levels, and there are separate categories for no added clinical value, negative added clinical value, as well as for non-documentable added clinical value (i.e. where the data quality is insufficient to determine the added clinical value).

Table 6.1: The Danish Medicine Council's six categories of added clinical value

Category	Clinical value
1	High added clinical value
2	Important added clinical value
3	Low added clinical value
4	No added clinical value
5	Negative added clinical value
6	Non-documentable added clinical value

Source: table by author based on Medicinrådet 2017

Briefly described, the DMC's approach evaluates the seriousness of different groups of outcomes. As an example, any statistically significant reduction in mortality (compared to the comparator treatment) will, as a minimum, result in a categorization of 3, low added clinical value. For less severe adverse outcomes, such as non-severe symptoms, side effects or other adverse events, there are more stringent requirements to be classified as having added clinical value.

While the DMC is reviewing the clinical evidence that is submitted, Amgros reviews the cost analysis submitted by the pharmaceutical company. The cost analysis describes the estimated financial impact of approving the medicine as standard treatment for the indications that have been applied for. These budget analyses do not just look at the price of the medicine in insolation, but also on the impact that using the medicine would have on other parts of the public healthcare system, as well as on directly measurable patient effects such as reduced travel time. Specifically, Amgros reviews whether the applicant has complied with the methodological guidelines that it sets out, the quality of the estimation models used, the degree of uncertainty that is associated with the estimates, and the quality of evidence that supports these different analyses (Medicinrådet, 2017).

Once the DMC has categorized the added clinical value, the process is continued by Amgros. If the medicine has been categorized as having positive added clinical value, Amgros will engage in a negotiation with the pharmaceutical company. The purpose of this negotiation, from Amgros' perspective, is to attempt to reach an agreement on a price that indicates "a reasonable relationship between the added clinical benefit of the medicine and the added costs of using the medicine, compared with current standard treatment" (Medicinrådet, 2017). The price that results from this negotiation is stated in pre-discount terms, and thus actual transaction prices (should the application be approved, and the drug sourced) may be lower as a result of subsequent negotiations. There is no clearly defined, publicly available definition of what constitutes a reasonable relationship between the different categorizations of added clinical value and the added cost, and so this determination is largely at the discretion of Amgros (Ibid.). It follows that for medicines classified as having no added clinical value (i.e., being directly comparable to the comparator treatment), the maximum allowable cost is zero, as any non-negative value would be less cost effective than the original comparator treatment. Amgros ultimately decides on either a positive or a negative opinion on the relationship between added clinical value and added cost (Medicinrådet, 2017).

The opinion by Amgros is not a final determination on the application, but rather a suggestion that is then reviewed by the DMC. Ultimately, the final decision lies with the DMC whether or not to

approve the pharmaceutical company's application for the medicine to be integrated into the Danish healthcare system. If the application is approved, the medicine will be defined as the standard treatment for the specific indication that was applied for. Unlike other health technology appraisal systems in other countries (e.g. NICE in the UK), there are no strict regulatory guidelines for how, or how quickly, the approval from the DMC should be actualized into treatment procedures throughout the country (Klein, pers. comm., March 22nd, 2018). Despite the lack of procedural guidelines, it is understood, based on interviews with the DMC (Ibid.) and the Danish Regions (Andersen, pers. comm. March 1st, 2018) that defined standard treatments are usually followed relatively closely, and that compliance with defined standard treatments therefore is not a major challenge. This is complemented by the fact that Amgros is responsible for not just negotiating the prices of the medicines, but also sourcing the medicines for the hospitals to use, thus having good insight into actual medicine usage.

6.2 Price cap agreements

A voluntary price cap agreement exists for hospital medicines in Denmark. This price cap agreement aims to contain the prices of medicines, such that medicine expenses do not suddenly spiral out of control, providing stability to the prices over time. The price cap agreement is negotiated between three actors: The Danish Association of the Pharmaceutical Industry ("Lægemiddelindustriforeningen" in Danish, or "Lif" for short) representing the manufacturers and sellers of medicines, and the Danish Regions and the Ministry of Health representing the buyers of medicine in the public healthcare system in Denmark (Lægemiddelindustriforeningen, 2016). Lif's members include 35 of the researching (i.e. not generic) pharmaceutical industry, including 8 of the top 10 global pharmaceutical companies by revenue (Lægemiddelindustriforeningen, n.d.; Statista, n.d.). There are many complexities to the agreements, but the main points are summarized in the following.

The current hospital medicines price cap agreement is effective from April 1st, 2016 and runs until March 31st, 2019. The scope of the agreement includes all hospital medicines sold by the members of Lif, covering a majority of hospital medicines sold in Denmark (Søndergaard, pers. comm., March 7th, 2018). Beyond the members of Lif, the Ministry of Health aims to include non-Lif members in the voluntary price cap agreement (Lægemiddelindustriforeningen, 2016).

The price cap agreement for hospital medicines has two main components which moderate prices: An external reference pricing system, as well as a built-in decrease over time. The external reference

pricing system mandates pharmaceutical companies to price each medicine at or below the average price of the same medicine in a range of selected countries. The basket of reference countries includes Sweden, Norway, Finland, the United Kingdom, The Netherlands, Belgium, Germany, Ireland and Austria (Lægemiddelindustriforeningen, 2016). Pharmaceutical companies under the price cap agreement must submit documentation for prices charged in the basket countries at anywhere from one to four separate points in time, depending on how many of the reference countries the medicine is already marketed in at the time of introduction into the Danish market. If the medicine is not marketed in any reference countries at the time of entry into the Danish market, then the introductory price (determined in negotiations with Amgros) becomes the temporary price cap. The price cap is then recalculated once the medicine is marketed in 3, 6 and finally all 9 basket countries. If the medicine is marketed in one or two reference countries at the time of entry to the Danish market, then the average of these reference country prices becomes the temporary price cap, with recalculations once the medicine is introduced into 3, 6 and 9 basket countries. No matter the timing of entry into the Danish market, it is not possible for the price cap to increase at any point of recalculation. If the new average is higher than the previous price cap (temporary or not), the previous price cap will be maintained (Lægemiddelindustriforeningen, 2016).

The second component of the price cap agreement is the negotiated decreases in the price cap over time. The parties of the current price cap agreement agreed on reductions in the price cap of every medicine of 2.5% at four points spanning the duration of the agreement, on May 1st, 2016; April 1st, 2017; April 1st, 2018; and finally, on February 1st, 2019. It should be noted that the price caps list the maximum allowed price before any discounts. Because Amgros achieves an, on average, approximately 30% discount compared to the listed price, these relatively small price cap decreases could theoretically be exceeded by the pharmaceutical company simply requiring lower discounts. However, it is written into the price cap agreements that the price cap reductions should be reflected in transaction prices and not be limited to formal price lists. Based on interviews with the Danish Regions (Andersen, pers. comm., March 1st, 2018), it is understood that compliance with this is adequate and that price cap reductions are generally met with drops in transaction prices.

7 Analysis of the Danish system for pricing medicines

This chapter analyzes the process of pricing a new medicine in the Danish public healthcare system. A focus is on identification of key problems and challenges that may hinder medicine affordability, access to medicines, and innovation. First, an overview of the methods used by the Danish

Medicines Council ("DMC") and Amgros is presented. Then, an overview of the main challenges related to the price cap agreement for hospital medicines is provided.

7.1 The methods of the Danish Medicines Council and Amgros

This section covers the methodology of the health technology appraisals and cost-effectiveness analyses of the Danish Medicines Council and Amgros. First, an overview of the competitive dynamics of a pharmaceutical across its life cycle, from patent protection to generic competition, is presented. Second, the issue of transparency in the evaluation of new medicines is brought up. Finally, the adverse effects of the Precautionary Principle of the Danish Medicines Council are illustrated.

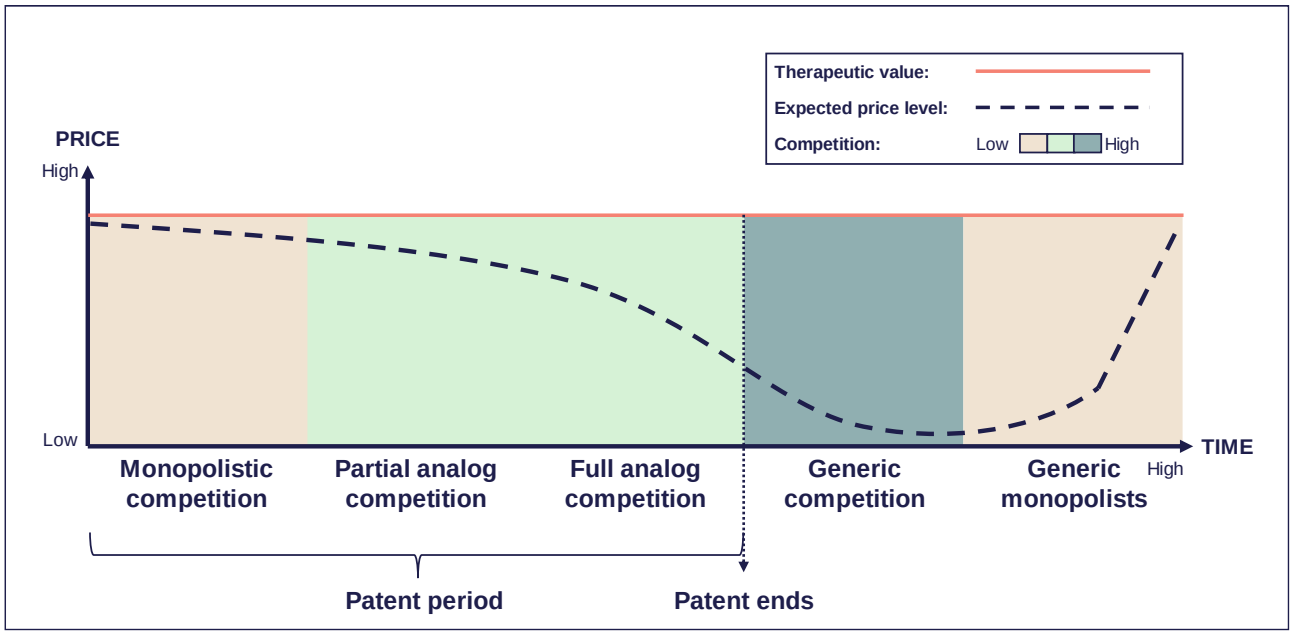
7.1.1 The competitive dynamics across a medicine's life cycle

In general, it is expected that prices of medicines to drop over time. This is due to the increased degree of competition that comes from the release of new medicines. The effect is especially significant when the patent of the innovator medicine expires, as it then becomes exposed to competition from generic producers. This part presents an overview of the competitive dynamics (market power of the branded pharmaceutical company and the expected price level) over the life cycle of a medicine. Furthermore, it is found that the optimal strategy for sourcing a medicine is dependent on the stage of the life cycle it is in.

7.1.1.2 Stages of the life cycle of a medicine

Branded pharmaceutical companies rely heavily on protection from competition through patents to be able to charge premium prices for their medicines. A study by Conti and Berndt (2014) found an average drop in price of medicines of approximately 40% following patent expiration. This is beneficial to payers, who can save significant sums by purchasing the new generic medicine, and to patients in countries that did not previously purchase the medicine, who are now more likely to be able to afford it. However, for the innovator company, this sudden drop in prices and revenues is a major challenge (Song & Han, 2016). Even if the medicine is not exposed to generic competition, the innovator company may find that its medicine is exposed to competition from other medicines that are structurally different, but have similar safety and efficacy profiles (Sonne, pers. comm., Feb. 2, 2018). This paper defines this as analog competition.

Figure 7.1: Overview of competitive dynamics



Source: figure by authors (2018) based on interview (Sonne, pers. comm., Feb. 16, 2018)

It is therefore possible to outline three main stages of competition that a medicine may be exposed to, as well as the resulting level of prices that are likely to be achievable by Amgros. These stages are illustrated in Figure 7.1. The first stage is *monopolistic competition*, wherein the pharmaceutical company markets a medicine that is patent-protected, and that is simultaneously the best (in terms of efficacy or safety) or the only treatment for the disease. The second stage is *analog competition*, wherein the medicine is exposed to competition from medicines that are structurally different from a chemical perspective, but have similar clinical effects. The third and final stage is when the medicine is exposed to *generic competition*, with generic producers introducing lower-cost medicines that are perfectly substitutable to the original medicine. It is generally observed that the medicine moves through the different stages throughout its life cycle (moving from less towards more competition) (Sonne, pers. comm., Feb. 2, 2018). In practice, the characterization into one of three stages is not always clear-cut, and especially the distinction between monopolistic and analog competition may be difficult to distinguish, and may be represented more accurately as a continuum. For this reason, the three categories are expanded with two sub-categories. For medicines exposed to analog competition, the dynamics of the competition may be significantly different depending on whether the comparator medicine is assessed as clinically similar, or if the innovator medicine is assessed as having small or moderate added clinical value. Furthermore, innovator companies that are exposed to generic competition may experience that generic prices become so low that it is unprofitable for the innovator firm to continue to produce the medicines. Berndt et al. (2007) found that when there are fewer than four producers of a generic medicine, the price difference compared to the branded medicine was

significantly lower. Having only a single supplier introduces even greater risk (Greene, Anderson and Sharfstein, 2016). For public medicine sourcing organizations such as Amgros, this presents a significant risk, as the single supplier status means the supplier becomes a *de facto* monopolist. This single-supplier case represents a specific sub-category of generic competition that this paper argues is necessary to categorize differently than one with multiple suppliers.

The different types of competition a medicine may be exposed to are associated with different levels of market power from the innovator pharmaceutical company's perspective. Market power is herein defined as the ability to price above marginal cost of production, in line with Cabral (2000). The following three sub-parts go through each stage of the competitive life cycle of a medicine, focusing on 1) the degree of market power of the innovator pharmaceutical company, 2) the expected price level of sourcing the medicine or its generic counterpart, and 3) the main challenges for Amgros and the DMC in sourcing and assessing the medicine. These findings are summarized in Table 7.1. The expected price level is listed as an absolute value. The categorization of each stage of competition, and the resulting market power and price levels, are primarily based on an interview with Flemming Sonne, CEO of Amgros (Sonne, pers. comm., Feb. 2, 2018).

7.1.1.2 Monopolistic competition

In monopolistic competition, legal exclusivity rights stemming from patent protection and the lack of analog competition provides significant market power. As mentioned, out of the approximately 3,000 medicines sourced by Amgros, the 100 most expensive medicines make up approximately 80% of the total hospital medicine costs. Furthermore, the 25 most expensive medicines account for between 40 and 45% of total hospital medicine costs. Thus, a very small proportion of the total number of products account for the vast majority of costs (Sonne, pers. comm., Feb. 2, 2018). For many of these very expensive medicines, the high price is caused by the existence of patents. Because the added clinical value provides the pharmaceutical company with the highest degree of market power in this stage of the medicine's life cycle, this paper categorizes the expected prices as very high to high (Ibid.), which is also illustrated in Table 7.1. From the perspective of Amgros and the DMC, the main challenge in this stage is to determine whether the price the pharmaceutical company is asking for their medicine is appropriate, given the assessment of added clinical value.

7.1.1.3 Analog competition

In analog competition, the innovator has reduced market power, but will typically have some degree of market power remaining. As mentioned, this paper differentiates between two types of analog

competition: Partial analog competition, and full analog competition. Under analog competition, the branded medicine is exposed to competition from a chemically different medicine, that nonetheless provides a comparable medical outcome. If the branded medicine is assessed as having important or low degrees of added clinical value (categories 2 and 3, using the DMC's categorizations of added clinical value), compared to the competitor medicine, this paper defines it as being exposed to partial analog competition. If the branded medicine is assessed as having no added clinical value (category 4 from the DMC), compared to the competitor medicine, this paper defines it as being exposed to full analog competition.

Under partial analog competition, the branded pharmaceutical company may still be able to exert significant market power. Due to the added clinical value, the medicine is in any case expected to be priced at a premium compared to its competition. The size of this premium will then depend on the categorization of added clinical value, as well as other factors, such as the type of disease. Thus, the price level is expected to be lower than that of a monopolist, as it is exposed to some competition, but higher than under full analog competition, as some market power remains (Sonne, pers. comm., Feb. 2, 2018). Like in the case of the monopolistic competition, the main challenge for Amgros and the DMC is to assess whether the price that the pharmaceutical company demands is justified by the added clinical value.

Under full analog competition, the market power of the branded medicine becomes more uncertain. If the analog competitors themselves are patent-protected, then the market of comparable medicines may not induce enough competition to significantly lower prices. This depends on the number of analogs that are considered comparable. Even in the case of generics, which are directly substitutable, Berndt et al. (2007) found that a minimum of four suppliers was generally required in order to see significant price drops compared to branded medicine. Thus, having a single or a few analog competitors may not reduce the market power of the branded pharmaceutical company significantly. For this reason, expected prices may range from medium (in the case of fewer suppliers) to low (in the case of more suppliers, or if a competitor loses patent protection). The main challenge for Amgros and the DMC at this stage is inducing and sustaining competition by ensuring that substitutable medicines are identified and included in tender offers.

7.1.1.4 Generic competition

Generic medicines are copies of branded medicines and are, by definition, directly substitutable for branded medicines. Active ingredients, dosage, form, and route of delivery must be the same as the

branded medicine (FDA, n.d.). For medicines exposed to generic competition, the market power of the innovator company is, theoretically, nonexistent, as the medicine is directly substitutable for a generic version. Nonetheless, the market power may remain or become high again if the medicine is not exposed to significant competition. For this reason, this paper divides generic competition into two sub-categories: Generic competition with multiple suppliers, and generic monopolists, with only one supplier of a generic product.

Under generic competition with multiple suppliers, the market power of the branded pharmaceutical company is either low or even non-existent. Song and Han (2016) note that once a patent expires, the pharmaceutical company can choose to "milk out" any residual market power, but this is a short-term approach and the company will need to invest additional resources to regain any market power. Nonetheless, in practice, the competitive effect of multiple generic producers on prices may take some time to be actualized. Thus, the pharmaceutical company may enjoy some degree of market power as the medicine is phased out. Once more than three generic suppliers have entered the market, prices are expected to drop sharply. For these reasons, this paper categorizes the expected price level as medium (with two or three suppliers) to very low (with many suppliers). The main challenge for Amgros and the DMC is, similarly to under full analog competition, ensuring that competition is induced by including all generic producers into tenders.

The specific sub-category of generic monopolists, where only a single generic producer is in the market, is especially concerning from the perspective of sourcing medicines. As competition drives prices down, approaching marginal costs, a singular supplier may end up supplying an entire market for a specific medicine. This is especially likely if the medicine is used to treat an orphan disease, as the patient population (and therefore the market size) is very small (Roberts, Herder and Hollis, 2015). Beyond the risk of delivery in the case of a production issue or accident (Sonne, pers. comm., Feb. 2, 2018), there are also significant adverse competitive effects to be considered.

When a generic producer becomes the single supplier of a medicine, they may use their *de facto* monopoly to increase prices dramatically, leaving sourcing organizations such as Amgros being forced to accept these dramatic price increases. This scenario happened in Denmark in January 2018, as a parallel importer of the labor-inducing medicine Syntocinon (a medicine developed in the 1950s) failed to deliver on the contract it had won in a tender offer. Amgros was forced to purchase the decades old medicine from CD Pharma, who had an exclusive sourcing agreement with the manufacturer, at a price that was 2,000% higher than the original contracted price. The Danish

Competition and Consumer Authority reported CD Pharma to the State Prosecutor for Serious Economic and International Crime following the incident, but ended up paying approximately 6 million DKK more than originally contracted over a six-month period (Medwatch, 2018).

The case of Syntocinon is not a unique one. In fact, this represents a challenge that has risen in importance in recent years. As Greene, Anderson and Sharfstein (2016) note, "*several pharmaceutical companies have developed a novel business strategy of dominating noncompetitive markets for older drugs and then increasing the price substantially*", citing among others the sudden price hike of isoproterenol (from 38 USD to 1387 USD), marketed by Valeant, which is not a member of the Danish Association of the Pharmaceutical Industry. Valeant was also the subject of a paper released by Roberts, Herder and Hollis (2015) after the company raised prices for trientine, a medicine used for the treatment of the orphan Wilson disease, by 1,300%.

Thus, this paper concludes that under generic monopolists, prices may be anywhere from very low (right after the second-last producer exits the market, following a period of very low prices) to very high (in cases where the non-competitive market is used to dramatically raise prices). The main challenge for Amgros and the DMC is to avoid the risks of having a single supplier, such as the risk of production malfunctions, as well as dramatic, sudden price increases.

7.1.1.5 Summary of findings

Table 7.1 summarizes the main findings of this section, noting that the degree of market power exerted by the branded pharmaceutical company varies greatly with the stage of the life cycle of the product. Furthermore, the expected price level is generally expected to drop over time, with the notable exception of under generic monopolists. Furthermore, the main challenge of the DMC and Amgros varies with the stage of the life cycle.

Table 7.1 Overview of findings across the stages of a medicine's life cycle

Competition	Characteristic	Innovator pharmaceutical's market power	Expected price level of sourcing medicine	Main challenge for Amgros and the DMC
Monopolistic	Important clinical value	High	Very high to high	Determining a fair price for the added clinical value
Partial analog	Important or low added clinical value	High to medium	High to medium	
Full analog	No added clinical value	Medium to low	Medium to low	Inducing and/or sustaining competition by identifying comparable medicines and including them in tenders
Generic	Multiple suppliers	Medium to low	Medium to very low	
Generic	Single supplier	N/A[6]	Very high to very low	Avoiding risks of having a single supplier

Source: table by authors (2018) based on Sonne (Sonne, pers. comm., Feb. 2, 2018)

7.1.2 Transparency in the Danish Medicine Council's and Amgros' methods

This part argues that there is a lack of transparency in the methods that Amgros and the Danish Medicines Council ("DMC") use to determine whether to approve a new medicine as standard treatment. The lack of transparency may exacerbate the already controversial topic of evaluating medicines. Furthermore, it is argued that increasing transparency of its methods may help secure the political foundation for the DMC, which is to be evaluated in early 2019.

7.1.2.1 The transparency problem

As outlined in Part 6.1.2, the processes that are involved in assessing the added clinical value and the cost-effectiveness of a new medicine are quite well-documented. The DMC provides detailed descriptions of their methodology and releases their decisions publicly soon after they are made (Klein, pers. comm., March 22nd, 2018). Similarly, Amgros provides detailed descriptions of the assumptions that are made, and the methods that are employed, when preparing the assessment of the cost analysis (Medicinrådet, 2017). Thus, there is significant transparency into the methodology employed in the health technology appraisal. However, this ends once the assessment of added clinical value is compared to the cost of the medicine. As mentioned in Part 6.1.2, the DMC first

[6] The innovator pharmaceutical company is, by definition, no longer present in the market at this stage

assesses a new medicine's clinical value compared to the relevant comparator. If the new medicine is found to have no added clinical value (i.e. it is clinically substitutable to the comparators), then it simply follows that the maximum price that Amgros would be willing to pay is what it is currently paying for the comparator medicine – any higher price would not be cost-effective. However, for cases where the DMC assesses the medicine to have an added clinical value, it becomes more difficult to assess what the appropriate value of this added clinical value is. One may argue that the only decision that ultimately matters is this final choice of whether or not to accept the relationship between added clinical value and the increased cost profile of the new medicine.

As mentioned in Section 6.1.2, Amgros aims to negotiate an agreement with the innovator company on a price that delivers "a reasonable relationship between the added clinical benefit of the medicine and the added costs of using the medicine, compared with current standard treatment" (Amgros, n.d.). However, this reasonable relationship remains undefined. Based on interviews with The Danish Association of the Pharmaceutical Industry (Clausen, pers. comm., February 1st, 2018), it is understood there may be some tacit knowledge within Amgros concerning appropriate price premiums (compared to the current cost) for different categorizations of added clinical value. However, if such guidelines exist, they are not publicly available. Thus, it is not immediately apparent to stakeholders outside of Amgros what constitutes a reasonable price for a medicine that has received one of the DMC's non-zero added clinical value categorizations (i.e. low, important, or high added clinical value). This lack of transparency stands in contrast with some other methods of assessing the appropriate price tag of a medicine, such as using the incremental cost-effectiveness ratio ("ICER") of the medicine. This methodology is applied heavily in the UK, where the effectiveness is measured quantifiably in quality-adjusted life years ("QALY") gained by the medicine versus the comparator medicine (Hill and Olsen, 2014). Based on interviews, it is understood that there is a consensus in the industry that the health technology appraisal organization in the UK, the National Institute for Health and Care Excellence ("NICE"), has a general limit of approximately £30,000 per gained QALY compared to the comparator medicine (Goldman, pers. comm., April 12th, 2018; Hedebye, pers. comm., March 23rd, 2018). This is not a strictly defined limit, and there are many exceptions, as well as factors that may increase this limit. However, it provides a baseline level that various stakeholders can expect to be compared to.

7.1.2.1 Benefits and disadvantages to the lack of transparency

It is argued that there are both benefits and disadvantages to the lack of transparency. One advantage, from the perspective of the DMC and Amgros, is the flexibility that is granted in terms of accepting or denying an application for a new medicine to become standard treatment (Klein, pers. comm., March 22nd, 2018). This paper argues that this is especially beneficial because the Danish Medicines Council is also mandated to take into consideration the Principle of Severity, and the Precautionary Principle. The Principle of Severity mandates the DMC to accept a higher price for a given added clinical value if the disease is especially severe. The Principle of Severity is implicitly implied in the evaluation of added clinical value, but may also be explicitly used, in which case it constitutes an intuitive, subjective assessment (Medicinrådet, 2017). The Precautionary Principle relates to taking extra precautions when considering treatments with large budget impacts, and the effect of this is analyzed in Part 7.1.3. Ultimately, both principles add complexity and subjectivity to an already complex analysis. Not having a quantifiable baseline of the maximum price may be a benefit, as the qualitative assessment and weighing of these Principles allows the Danish Medicines Council flexibility to consider these to the degree they find reasonable.

However, this paper argues that the lack of transparency comes at a price, as stakeholders with an interest in decisions regarding the medicine may lack insight into the reason for the acceptance or denial of the application to recommend the medicine as standard treatment. These stakeholders include the pharmaceutical company, which naturally has an interest into understanding why its medicine is either accepted or rejected (and an interest in being able to forecast the likely outcome); and the patients, who are left without access to potentially life-changing medicine if the medicine is rejected as standard treatment.

For the pharmaceutical company, having insight into the expected price the company will be able to charge for its new medicines may reduce the riskiness of developing new medicines, incentivizing further innovation. As Dana Goldman, Director of the University of Southern California's Schaeffer Center for Health Policy and Economics, phrases the notion an interview with the authors of this paper, "*any time you can reduce uncertainty, you are going to help patients*" (Goldman, pers. comm., April 12th, 2018). From the perspective of patients, it may be particularly disturbing to see a medicine be rejected if there are no clearly defined guidelines for how new medicines are assessed. This criticism was put forth by the head of the organization that represents patients suffering from spinal muscular atrophy ("SMA") in Denmark (Muskelsvindfonden), Henrik Ib Jørgensen. Henrik was

interviewed concerning the case of nusinersen, commercially marketed as Spinraza by Biogen for the treatment of SMA (Jørgensen, pers. comm., March 9th, 2018). Spinraza is the first medicine that the DMC denied to recommend as standard treatment after the Council was introduced in 2017. The denial of the application has sparked a great deal of controversy in Denmark, and this paper argues that the lack of transparency of how the application was assessed has been an exacerbating factor in this controversy. Beyond criticism from patient organizations (Danske Patienter, 2018; Muskelsvindfonden, 2018), the decision also invoked public criticism from prominent members of the Danish parliament, including Liselott Blixt, Member of Parliament for the Danish People's Party and Head of the Danish Parliament's Committee on Healthcare (Sundhedspolitisk Tidsskrift, 2018). This paper argues that, as the DMC is still in its infancy, it is essential that the organization is allowed to operate independently from the influence of politicians. This notion is also put forth by Kjellberg (Kjellberg, pers. comms., April 4th, 2018) in an interview with the authors of this paper. If the DMC had been able to provide quantitative arguments for denying the application for Spinraza in the specific case, the DMC might have been in a better position to defend its decision by comparing the cost to well-established guidelines in similar countries, like the UK.

Overall, this paper argues that having less transparent assessment guidelines concerning the acceptable premiums for added clinical value may make it slightly easier for the DMC to assess medicines. However, it also comes with significant disadvantages. Having more transparent guidelines would reduce uncertainty concerning the appraisal of new medicines, encouraging new innovation. Furthermore, increased transparency in appraisals may reduce the controversy stemming from future denials, securing the long-term stability of the current assessment model, decreasing the political uncertainty going forward. This is considered especially relevant in light of the fact that the DMC is up for review by 2019.

7.1.3 The effect of having a precautionary principle

This section covers the Precautionary Principle, which, despite its sound intentions, is found to have significant adverse effects, both in terms of static and dynamic efficiency. The Principle may directly lead to less optimal utilization of resources on medicine, but also disincentivize the pharmaceutical industry from developing medicines that seek to cure or treat diseases with large public health implications.

7.1.3.1 Describing the Precautionary Principle

When the Danish Medicines Council ("DMC") assesses a new medicine, one of its considerations includes the Precautionary Principle. This principle provides the DMC with two mandates. The first is that the DMC should take extra precaution when assessing medicines that are likely to have a high budget impact (Medicinrådet, 2017). Because new medicines are priced according to the added clinical value they bring compared to the current medicines, it follows that the most expensive medicines are those that are very effective compared to current treatments. Since the total budget impact of implementing a new medicine is necessarily equal to the additional cost (compared to the current treatment) multiplied by the volume of the medicine, the budget impact will also be proportionally higher the more patients are treated with the medicine. Thus, the medicines with the highest budget impact will be the medicines that are significantly innovative and target a broad patient population.

The second mandate granted to the DMC through the precautionary principle is to avoid allocating excessive funds in the direction of one type of medicinal treatment or towards any one disease. The principle is sound from a perspective of budgeting – many newly developed medicines can cost hundreds of thousands if not millions of Danish kroner per patient per year, and administering and prescribing such an expensive medicine to thousands of patients can have an enormous and very sudden immediate impact on the budget for medicines.

7.1.3.1 The effects of the Precautionary Principle

Even a medicine with a small patient population can have a large budget impact. In 2017, Amgros evaluated the cost of implementing nusinersen, marketed as Spinraza by Biogen for the treatment of spinal muscular atrophy, as standard treatment in the Danish healthcare system. It found that approving the medicine as standard treatment was expected to lead to a yearly additional cost of approximately 250 million Danish kroner per year, despite the patient population only consisting of approximately 160 patients (as the disease is very rare) (Medicinrådet, 2018). It is stated by Amgros that this additional cost is mostly driven by the cost of the medicine (Ibid.). This number should be compared to a total spend on hospital medicines of around 8 billion Danish kroner (Albinus, 2018). The medicine in question was not approved as standard treatment, but had it been, the treatment would have added around 3%[7] to the total hospital medicine budget, to treat fewer than a few hundred people. Because of the small patient population, the DMC did not find reason to include the precautionary

[7] 250 million DKK represents 2.96% of the 2017 hospital medicine expenditures of 8.445 billion DKK

principle in its evaluation of nusinersen (Spinraza) (Medicinrådet, 2018). Nonetheless, it is apparent that even a medicine targeted at a small population may be extremely costly to introduce.

In fact, as of May 2018, the precautionary principle has not been applied directly in the evaluation of any new medicine. However, the precautionary principle was mentioned during discussions concerning the development of a new treatment guidance for hepatitis C (Medicinrådet, 2017). Many new and expensive, yet also highly effective, medicines to treat hepatitis C have been developed within recent years. The price for these medicines is approximately 300 to 500 thousand Danish kroner per 12-week, usually curative, treatment (Albinus, 2018). Furthermore, the patient population is quite significant. It is estimated that there are approximately 21,000 hepatitis C patients in Denmark, with about 7,000 of those with a diagnosis and 5,500 receiving treatment (RADS, 2016). While the treatment guidance for hepatitis C by is still being developed by the DMC as of May 2018, even cautious assumptions about how these expensive medicines are to be administered provides insight into why the precautionary principle may be relevant to consider. In 2016, RADS, one of the precursors to the DMC, recommended that 70% of the patient population should be treated with Viekirax, a treatment with a list price of 397 thousand DKK. Even assuming significant (e.g., 30%[8]) discounts in the transaction price achieved by Amgros, treating this proportion of the diagnosed population would cost more than a billion DKK[9]. Because the treatment is so expensive, it is currently only provided to those with progressive symptoms (McColough, Bloch and Leuchter, 2017). Based on interviews with The Danish Assocation of the Pharmaceutical Industry, it is understood that similar limitations have been implemented in the UK through NICE, despite the treatment being cost-effective even for those without progressive symptoms (Clausen, pers. comm., February 1st, 2018).

Given the extremely high and immediate costs of treating a widespread condition with such expensive medicines, it seems reasonable to implement limitations on the usage and administration of similar medicines. However, there are important direct and indirect problems that occur as result of such limitations. The direct adverse effect is the inefficiency of avoiding a cost-effective treatment. In the case of hepatitis C, multiple studies find that while up-front costs to treat the disease using new, advanced treatments are very significant, there are large health benefits stemming from immediate and extended treatment (Nuys et al., 2015; Sbarigia et al., 2017; Goldman, Chandra and Lakdawalla,

[8] Slightly above Amgros' average discount rate
[9] A list price of 397 thousand DKK, with a 30% discount, multiplied by 70% of the 5,500 diagnosed patients equals 1.069 billion DKK

2014). Because the disease is contagious, and the treatment curative, expanding and accelerating treatment can dramatically reduce the incidence of the disease in the population, generating significant cost savings by eliminating the need for future treatment for those who have been cured. Beyond the economic return, it goes without saying that providing advanced treatment to a large group of patients provides a massive increase in the quality of life of patients and represents a significant boost in welfare.

There is also an indirect, adverse effect of limiting access to expensive, broad treatments like the advanced treatments for hepatitis C. Having the Precautionary Principle disincentivize pharmaceutical companies from developing medicines that are both highly innovative (measured by the added clinical value) and simultaneously target broad populations, as these will have the largest budget impact. These medicines will face difficulty in being adopted into healthcare systems. For this reason, Dana Goldman, Director of the University of Southern California's Schaeffer Center for Health Policy and Economics, notes in an interview with the authors of this paper that many pharmaceutical companies are focusing to a higher degree on developing new orphan drugs (Goldman, pers. comm., April 4th, 2018). These medicines are used in the treatment of very rare diseases. While these medicines are typically very expensive, the low patient populations make it easier for public healthcare systems (and their health technology assessment organizations) to accept the medicines. Similarly, developing new curative treatments for common (and, especially, contagious) diseases becomes relatively disadvantageous. Because curative treatments of contagious diseases diminish the basis for recurring revenue by successful treatment, payments to innovator companies occur only for a short period of time. The cost of the medicine is spread out over a very short period, compared to medicines that are used continuously, creating large up-front costs for payers. But this is misaligned with the incentives of the precautionary principle and similar mechanisms, as large and sudden costs towards one area of therapy are avoided. This may represent a significant efficiency loss over time, as newly released medicines potentially target smaller and smaller patient populations, limiting the broad medical advances. One may even argue that the largest potential future public health advances are directly disincentivized by the current precautionary principle.

7.2 The effectiveness of price cap agreements

As outlined in Section 6.2, medicine pricing in the Danish public healthcare system is affected by the existence of voluntary price cap agreements between the pharmaceutical industry and the payers. Having accounted for the mechanisms of the price cap agreements, it is observed that there are

problems with the way these agreements are constructed. In this section, this paper argues that some of the mechanisms of the price cap agreements may hurt access to medicines, reduce the ability for pharmaceutical companies to apply real world evidence in pricing their medicines, and that the price cap agreements may, in fact, be ineffective at limiting excessive prices for medicines.

7.2.1 Limiting price increases may disincentivize post-market studies

One of the issues with the price cap agreement is the inflexibility that is offered in terms of raising the price of a medicine once the medicine has been adopted into the Danish healthcare system. The agreement dictates that prices cannot rise above the introduction price at any point under the duration of the agreement. This price limit is set at the price that is submitted to the Danish Medicines Council ("DMC") and Amgros for assessment. At first glance, it seems highly reasonable to enforce such a limit on prices, since this ensures some degree of stability of prices. Furthermore, this price cap, all else equal, ensures that price are only driven by new medicines, and not by existing medicines. However, being unable to charge higher prices over time becomes an issue in certain cases.

If the pharmaceutical company completes post-market studies aimed at discovering the effectiveness and safety of the medicine outside of strictly controlled clinical studies, this data may show significantly different results than those in clinical studies. If these results turn out to be better than expected (based on results from clinical trials), the pharmaceutical company may reasonably wish to raise prices. Given that the actual added clinical value of the medicine is now demonstrably higher, a larger price would also be accepted by the DMC. Even seeing similar results in real-world settings as those documented in randomized controlled trials may be valuable for the pharmaceutical company and its ability to price its medicine, as this would demonstrate external validity of the clinical studies. This paper looks more closely at the benefits and challenges of applying real-world evidence in the pricing of medicines in Part 8.4.3, but argues that the current structure of disallowing price increases over time, *ceteris paribus*, disincentivizes pharmaceutical companies from completing expensive post-marketing studies. This adversely affects not just the pharmaceutical companies, but also patients and payers, as the real-world effectiveness of the medicine is less clear.

7.2.2 The frequency of benchmarking in external reference pricing

The external reference pricing mechanism that is included in the price cap agreement (described in Section 6.2) has another significant limitation: it is only calculated anywhere from one to, at most, four times during the life cycle of the medicine, despite one expecting the medicine to have very dramatically different prices over time. As the final price cap calculation is performed once the

medicine in question has been marketed in all nine of the reference countries, the price cap will only marginally decrease following this point in time (Lægemiddelindustriforeningen, 2016). There are at least two issues with this.

First, because pharmaceutical companies regularly perform strategic and staggered product launches (Persson and Jönsson, 2016), the competitive dynamics may differ significantly from country to country. If the branded medicine becomes exposed to extensive analog competition in a reference basket country, the prices of the branded medicine would likely drop markedly. But, under the current structure of the price cap agreement, this drop may not even be registered. In this case, the price cap agreement becomes ineffective and arguably even pointless.

The second issue occurs if market competition drives the price of the branded medicine significantly below the price cap (which only drops marginally after being introduced into the ninth reference country). In this case, the price cap remains artificially high, giving plenty of room for the transaction price to vary without being limited by the price cap. Thus, the stabilizing effect of the price cap agreement disappears.

There are additional problems associated with using external reference pricing that are not specific to the Danish public healthcare system. These are covered in Section 10.2.1.

7.3 Chapter sub-conclusion

This chapter identified five key challenges. The first two challenges are related to the competitive dynamics across the life cycle of a medicine. The first identified challenge concerns how Amgros and the Danish Medicines Council ("DMC") can determine whether to accept a price for a medicine, given its added clinical value compared to its competitors. The current methods used to evaluate medicines lack transparency and may hurt the sustainability of the model. Thus, the first challenge may be stated in the form of a question as "How can medicines be priced in order to rationally contain costs?[10]".

The second identified challenge is that of generic monopolists, and the significant risks associated with these, especially deliberate price gouging. This challenge may be stated in the form of a question as "How can the risks of price gouging from generic monopolists be mitigated?".

[10] *Rationally containing costs* is defined as a concept in Section 2.3

The third identified challenge relates to the use of the Precautionary Principle by the DMC, and its direct and indirect adverse implications. This challenge may be stated in the form of a question as "How can the Danish Medicines Council ensure that broad public health advances are incentivized?".

The fourth and fifth challenges both relate to the price cap agreement. The fourth challenge concerns the inability of prices to rise under the agreement, disincentivizing post-market studies. This challenge may be stated in the form of a question as "How can the adverse incentives of the price cap agreement be mitigated?".

The fifth and final identified challenge is the ineffectiveness of the external reference pricing mechanisms in the price cap agreement. The frequency of the benchmarking is too low, making the model ineffective in many cases. This challenge may be stated in the form of a question as "How can the price cap agreement be structured, such that it remains effective over time?".

8 Value-based pricing

8.1 Introduction

Pricing has historically been neglected in both academia and by managers, compared to other parts of the marketing mix (Hinterhuber, 2004). However, *value-based pricing* ("VBP") has been noticed recently for its ability to improve profits for companies. Because price is a more impactful lever than most other commonly used managerial profit goals, such as reducing fixed or variable costs, the stakes are high when it comes to setting optimal prices, thus making VBP an effective tool in this regard (Ibid.). In the same way that corporations are finding VBP more interesting and useful, government institutions are also seeing the value of implementing VBP. In England, VBP was implemented through the *National Institute for Health and Clinical Excellence* ("NICE") in 1999. Following this, Germany passed the reform "AMNOG" in 2010. Similarly, Denmark recently established the Danish Medicines Council in 2017 (Sieler et al, 2015). In conclusion, VBP has a growing impact among European healthcare systems, and the real impact of applying VBP is therefore important to understand.

In the following section, different aspects of VBP will be discussed thoroughly. First, this paper sets out a definition for VBP. Second, the benefits and challenges of applying VBP in a healthcare context will be presented. This will be followed by a description of the methodology and a comparison between VBP measurement through *randomized clinical trials* ("RCT") and *real-world data* ("RWD"). After this, it will be shown how risk-sharing agreements may be used as a tool under VBP. Finally, the English healthcare system will be visited, where the focus will be on how England applies VBP through health technology appraisals and the measure of *quality-adjusted life years* ("QALY"). The conclusion of the findings will then be applied in Chapter 11 to form recommendations to determine the ideal conditions for implementing VBP models.

8.2 What is value-based pricing?

In a healthcare and pharmaceutical context, value is derived from achieving the highest possible health outcomes or gains for patients, measured against the total cost of care. Hence, it is defined as healthcare treatment outcomes relative to their cost. More precisely, VBP refers to the regulation of reimbursement or pricing of medicine based on its therapeutic value (Porter, 2010; Sussex et al, 2012; KPMG, 2016; Grandjour, 2017). The World Health Organization notes the following on VBP: "*The concept of value-based pricing has gained momentum, though there is no widely accepted definition of value. In general, it is meant that countries set prices for new medicines and/or decide on*

reimbursement based on the therapeutic value which medicine offers, usually assessed through health technology assessment or economic evaluation." (Vogler and Zimmerman, 2016, p. 118). The central principle of VBP is that the costs of medicines cannot exceed their health benefits (Gandjour, 2012).

8.3 Value-based pricing – benefits and challenges

Reasons to advocate for the application of VBP in the healthcare system include the ability to control rising prices amongst new medicines and prevent unreasonable premiums for medicines which offer limited incremental therapeutic value over existing drugs – *me-too medicines* (Hill and Olsen, 2014).

There are four main advantages related to VBP (see Table 8.1):

Table 8.1: value-based pricing – benefits and challenges

Benefits	Challenges
• Lowers incentives for me-too medicines • Creates incentives for innovation • Directs pharmaceuticals' innovation • Aligns incentives of payers and pharmaceuticals • Perceived as "fair"	• Measuring value of medicine can be challenging • Data sources must be chosen carefully • Changing evidence base hard to follow-up on • Not effective under generic competition • Concept of VBP can be misunderstood • Does not consider affordability

Source: table constructed by authors (2018) based on chapter findings

1) *VBP prevents purchases of me-too medicines, which provide minimal incremental value.* Applying VBP forces the user to look at the actual value created by the medicines, rather than blindly buying the latest developed medicine for any costs. This can help users prioritize the budget and avoid wasteful spending on me-too drugs. In addition, me-too medicines can also divest R&D investment away from real innovation, and limit penetration from generics (Régnier, 2013).

2) *VBP creates incentives for the pharmaceutical industry to focus on real breakthrough medicines.* The underlying rationale is to incentivize genuine innovation by connecting buyers' willingness to pay to the "additional value" created (Jayadey and Stiglitz, 2009; Webb, 2011; AAFP, 2016).

3) *VBP can help make the valued features clearer, therefore directing the innovation and investment.* Using the principles of VBP to establish clear measures of what the payer values can help direct pharmaceuticals' resources and research efforts towards developing more targeted treatments (away from unrewarded areas) (Deloitte, 2012).

4) *VBP aligns the incentives of the pharmaceuticals with the payers*. When patient value equals the price of medicine, the incentives of payers and suppliers are aligned (Deloitte, 2012).

5) *VBP is perceived as a "fair" pricing model for both payers and suppliers*. Given that payers only pay for received value, VBP is perceived as being fair (Goldman, pers. comm., April 12, 2018).

VBP also poses challenges which may be classified into six underlying categories (see Table 8.1):

1) *It can be difficult to measure the value of medicines.* One initial question that arises is how to measure value. Measuring value can be extremely difficult, as small differences in assumptions can give big different estimates of how cost-effective a therapy is. These assumptions can include treated population size, treatment duration, and effectiveness of therapy (Goldman and Anupam, 2017).

2) *Data sources have a large impact on the results, and it can be difficult to select a source.* Clinical trials differ a lot from real-world treatment settings. Thus, the selection of the data source used to evaluate cost-effectiveness can lead to different results with respect to cost-effectivity (Ibid.).

3) *Changing evidence base.* New studies are continuously conducted in larger populations, leading to newly discovered evidence. However, the healthcare system is generally slower to incorporate the new findings. Hence, coverage can be based on outdated data (Ibid.).

4) *Not effective when generic competition enters the market.* When the patent on branded medicines runs out, generic competition enters the market. One of the great advantages of VBP is that it rewards innovation, but this does not apply when generic medicines copy pre-existing treatments. Therefore, VBP is less effective in lowering prices in a market saturated with generic medicines (Ibid.)

5) *Concept of VBP can be misunderstood.* A medicine's budgetary impact is sometimes misconstrued with its value. Medicines with large effects on budget are at times deemed less intrinsically valuable, despite the possibility that it might be highly effective (Ibid.).

6) *Affordability is not considered*. A major risk of using VBP as the solitary basis for pricing is that it does not consider affordability. A medicine might offer large health benefits or high value, but the costs may not be affordable (Garnet et al, 2017).

From findings above, the following conditions of when payers should apply VBP have been identified:

1) Desire to maximize health outcomes given a limited budget
2) Expenditure increase due to me-too medicines, or the government wishing to avoid paying premium for me-too medicines
3) Lack of innovation or a need for more innovation from pharmaceutical companies
4) Sufficient government resources to implement a health technology appraisal institution

5) There is a high degree of competencies in terms of understanding the pros and cons of VBP to avoid common pitfalls
6) Branded patented medicine market with no infiltration of generic medicines

These conditions should be considered when VBP is being applied. It is important to note that these conditions are not meant to be defined "laws", but rather indicators of whether or not VBP is suitable in the situation.

In conclusion, VBP disincentivizes me-too medicines, supports innovation, and aligns incentives of payers and pharmaceuticals. However, value can be difficult to measure, and many factors such as data sources, changing evidence base, and falling prices can make it difficult to apply VBP correctly. To adopt VBP and access its full potential to support innovation and align incentives, the application of VBP must be executed in a manner which clearly sets out parameters for its evidence base, value measurement, and data sources. Thus, VBP seems to possess great benefits, which can help overcome topical challenges in healthcare systems, but implementing it and using it in practice can be challenging and it is important to understand the challenges to navigate around them.

8.4 How to measure value?

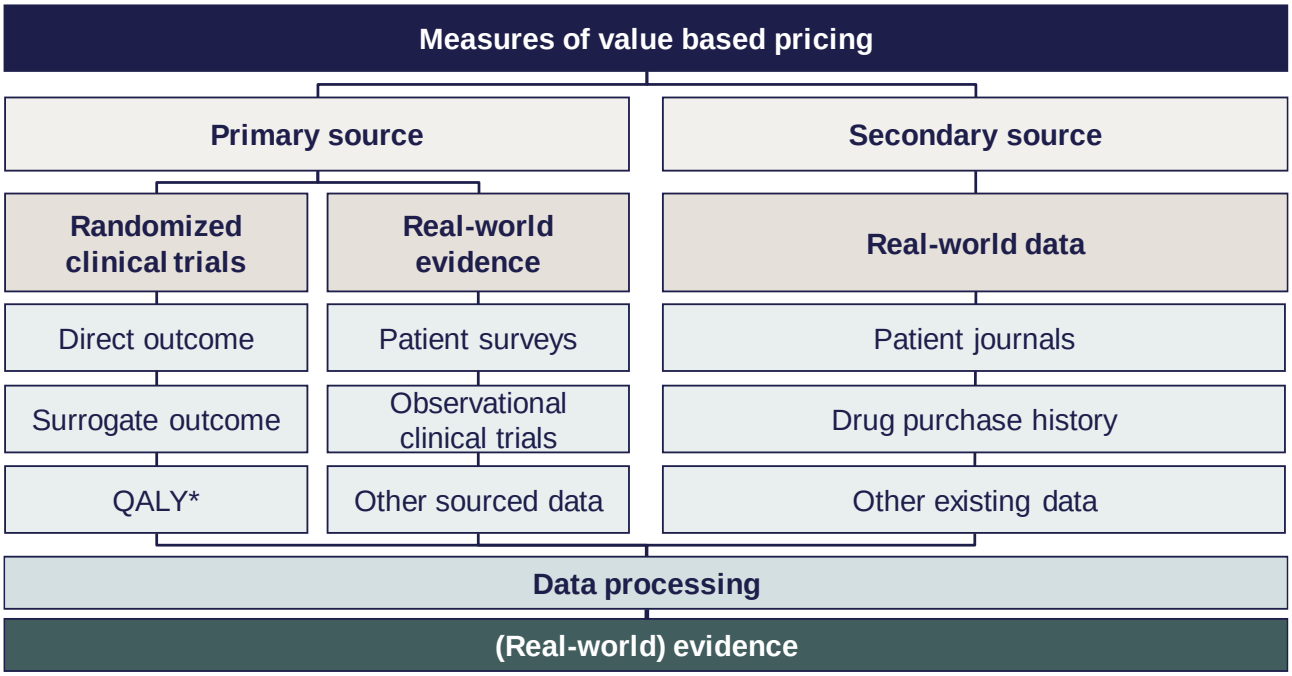
The value of VBP is measured based on data, which can be collected by primary data collection and secondary data collection as illustrated in Figure 8.1. Within primary data collection, there are mainly two methods: *randomized clinical trials* ("RCT") and *real-world evidence* ("RWE") collected from a primary source. In contrast, secondary data collection consists of *real-world data* ("RWD"). Once the data are collected and analyzed through the different methods, the final results can be applied as evidence, which can be used for decision-making in a VBP context.

RCT is defined as a study where participants are divided by chance into separate groups that compare different interventions. Dividing people into groups by chance means that the groups will be similar and the effects of the treatments they receive can be compared more fairly (NCI, 2018). RCT can give strong data on the efficacy of treatments rather than on effectiveness (Makady et al., 2016).

RWE and RWD are defined as "*data used for decision-making that are not collected in conventional RCT".* Even though, RWE and RWD are often used interchangeably in clinical R&D, they are not the same. RWD is secondary data collection, where the data used are data that have already been collected for another purpose (e.g. administrative patient journal keeping, hospital data, data from clinicians etc.). This is a benefit of secondary data collection, as it allows for very large amounts of

data to be collected relatively easy. If value shall be derived from RWD, one must analyze and select pertinent aspects of the RWD so it can be applied as RWE. Hence, RWE is a product of analyzed. RWD and can generally be recognized as the most important conclusions that could be derived RWE can then be used to determine important aspects such as the value of a medicine (Jones, 2016).

Figure 8.1: overview of value-based pricing measures



Source: figure by authors (2018) based on interview (Hammer-Helmich, pers. comm.; March 13, 2018)

However, RWE can also be a form of primary data collection for a predetermined purpose. Examples of RWE with primary data collection are post-market surveys or observational trials. In these cases, an analyst would determine the purpose of the study and the metrics through which the outcome could be measured. The analyst could then observe a patient group, which is already being treated with the medicine, and simply observe the outcomes without any intervention. Through this methodology, these studies would also be considered to generate RWE (Bate et al., 2016; Jones, 2016; Hammer-Helmich, pers. comm., March 13, 2018). However, this paper will solely reference RWE as evidence derived from secondary sources of RWD.

This paper will only consider RCT and RWE based on RWD. Due to the overlapping characteristics between the three methodologies, the paper focuses on the two most distinct measures to cover a wider range of procedural methods. Furthermore, RWE derived from RWD is becoming more relevant in the pharmaceutical industry as it can be less resource intensive and is regarded as a more advanced computing approach. Figure 8.2 shows an overview of the three types of measures. RWE

based on primary data have overlapping characteristics from both RCT and RWE derived from RWD. However, RWE based on primary data also have its own unique characteristics, this is why it is placed in between the two, where the white color in the middle represents its unique characteristics (Hammer-Helmich, pers. comm., March 13, 2018).

Figure 8.2: type of value-based pricing measures

Source: *figure by authors (2018) based on interview (Hammer-Helmich, pers. comm.; March 13, 2018)*

The following sections will explain and compare RCT and RWD measures in the light of VBP.

8.4.1 How can randomized controlled trials be used in assessing value?

Results from an RCT are used in VBP, often through healthcare-related quality of life ("QoL") scores (Ogden, 2017). QoL is commonly incorporated into the design of clinical trials as a primary or secondary outcome (Lemieux, 2011). As an example, the QoL score is used to derive the *quality-adjusted life years* ("QALY") in health technology appraisals (Ogden, 2017). QALY and QoL will be further elaborated on in Part 8.6.4. RCT applications in VBP largely depend on the criteria of health technology appraisals. Apart from QoL scores, the efficacy and health outcomes are also evaluated in health technology appraisals using RCT (Ogden, 2017).

8.4.2 How can real-world data used in assessing value?

RWD has become a popular topic in the pharmaceutical industry, mainly due to the advancement in computing in recent years (DIA, 2016). This has allowed collection, sharing, and analysis of large quantities of data routinely at a relatively low cost, which was previously uncommon. This increased use of technology has changed the ways in which patient level information is collected, stored, and used, thus increasing the potential of RWD (Holtorf et al. 2008; Miani et al., 2015; DIA, 2016).

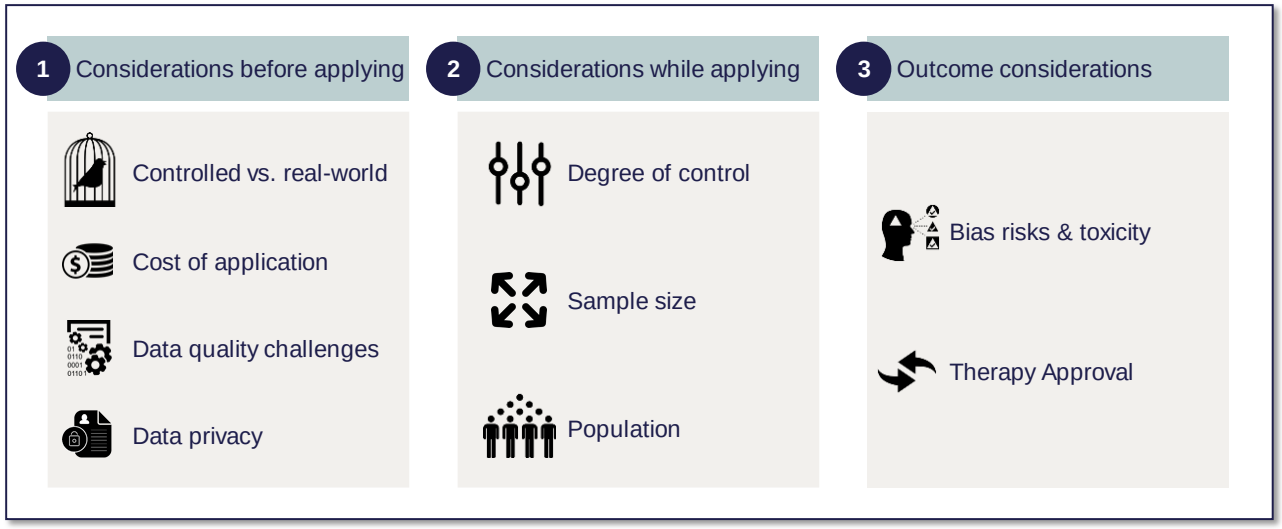
RWD can support VBP as it can be used in health technology appraisal. For example, when RCT evidence on a medicine's efficacy is lacking, it can be difficult to assign a fair value to the medicine. This is where RWD can be used to support the lacking evidence. RWD can also be used to provide information on effectiveness estimates, thereby allowing indirect comparisons of treatments. There are also cases where RWD can be used to support RCT data on treatment effects where data on specific subpopulations or long-term follow-up are inadequate (Makady et al., 2017). In addition,

many analysts and researchers believe that RWD has great potential to improve the method used for drug discovery and development (DIA, 2016).

8.4.3 Comparing randomized controlled trials with real-world data

The following section will walk through the strengths and weaknesses of both RWD and RCT. The structure of the discussion can be seen in the Figure 8.3. Thus, this section covers (1) considerations before applying, (2) considerations while applying, (3) outcome considerations. An overview of the comparison between RCT and RWD can be seen in Table 8.2.

Figure 8.3: structure of comparison between RCT and RWD



Source: figure by authors (2018) based on chapter findings

8.4.3.1 Considerations before applying

Controlled vs. real-world:

RCT is the gold standard but has uncertainty concerning internal validity.

RCT is currently seen as the gold standard for rational therapeutics in evidence-based medicines (Gyawali et al., 2017). It is an important instrument for conducting scientific evidence on the efficacy and safety of medicines, while giving an understanding of the biologic mechanisms involved in its therapeutic action. RCT is crucial as it is designed to give important premarket evaluation, which is strong evidence that a medicine could "work" (Sherman et al., 2016). RCT is also used in most health technology appraisals to determine whether medicines are cost-effective and should be reimbursed (Ogden, 2017). Nevertheless, the internal validity reached in RCT is often attained at a cost of ambiguity about generalization, mainly as the populations can differ significantly from those in the real world (Ibid).

RWE can offer a realistic picture from the real-world of a treatment

Contrary to RCT, RWE can contribute to a more realistic picture of what a treatment can offer its patients, simply because it reflects the real world, and not a strictly controlled environment (Makady et al, 2018). Data obtained from RWD can show whether a treatment has succeeded in creating value for patients. For instance, patient journals can reveal whether a patient has been cured from a certain disease after taking medication. Additionally, the study by Dilokthornsakul, Chaiyakunapruk and Campbell (2015) showed that asthma studies that used RWD were twice as likely to judge a treatment as cost effective as those using clinical trial data only. This indicates that there could be a meaningful difference between using RWD relative to using RCT as data source (Goldman and Anupam, 2017).

Cost of application

RCT is very costly. RWE has lower marginal cost but can be costly to implement initially.

It is claimed that RWE is less costly to use compared to RCT (Gyawali et al., 2017; Rassen, 2017). Conducting RCT can be costly, and the expense of conducting RCT has been growing steadily for years (Sherman et al., 2016). Costs can be as high as 1 billion USD (about 6.2 billion DKK), therefore its feasibility for every healthcare intervention can be questioned (Gyawali et al., 2017). RWE can have lower incremental costs relative to RCT because the data already exist and do not need to be re-created. Nevertheless, the cost of using RWE also depends on the cost of data preparation.

Ideally, RWD should be easily drawn from a database and analyzed by an analyst or machine learning algorithm to give RWE and insights on cost effectiveness (Ibid.). However, the process of analyzing RWD might be considered far from ideal as there are many hurdles that must be overcome in order to obtain valuable RWE. The following are some examples of why RWD is not fully utilized and implemented today (Miani et al., 2014): *the lack of standardization in terms of content and data quality*. More specifically, common terminology standards are lacking; existing data remain incomplete and data quality assurance systems remain underdeveloped. *The lack of shared standards in terms of governance structures*. Data are often only granted in academic research and there is a lack of clear accessible pathways, thus making it difficult to access data (Ibid.).

Although the incremental costs of analyzing RWD might be less costly than cost of conducting RCT, the initial investment of implementing and standardizing RWD may be substantial. This is supported by scholars and the interview with Samuelsen, Global Project Director at Novo Nordisk with an

expertise in regulatory aspects of using real world evidence for drugs (Miani et al., 2014; Gyawali et al., 2017; Samuelsen, pers. comm., March 22, 2018).

Data quality

RWE's data quality can have credibility issues as data quality and statistical validity is questionable. RCT does not have the same challenge.

Often, working with RWD and RWE also means working with big data which uncertain levels of quality. This, combined with a shortage of researchers with appropriate methodologic knowledge, can result in poorly conducted studies and analytic designs which generate unreliable and incorrect conclusions with questionable statistical validity (Sherman et al., 2016; Gyawali et al., 2017). Miani et al., (2014) also pointed out that *methodological challenges limit efficient use of RWD.* Methodological challenges make it difficult to collect and use RWD efficiently (e.g. analytical capabilities are limited) as there are fragmented systems across countries (Miani et al., 2014).

When processing RWD, analysts must use the data already available. In the case of limited data and measures that correlate with health outcomes, data analysts must create proxies and assumptions to do proper health technology appraisals. As an example, an analyst may have pharmacy data on patients buying one type of medicine. A proxy could be that if the patients have stopped using the medicine after 3 purchases, then it is a result of no efficacy. However, it is not entirely known for certain why the patient stopped buying the medicine. Therefore, it can be difficult to capture the entire "truth" through RWE, and there are uncertainties which make it difficult to get confirmation. The interviews conducted with Hammer-Helmich and Peterson also further solidified the importance of having clear-cut measures if RWE should be used in health technology appraisals (L. Hammer-Helmich, pers. comm., March 13, 2018; K. M. Pedersen, pers. comm., March 21, 2018).

In contrast to RWD, RCT does not face the same challenges because it is conducted during a treatment process and it would possible to go back to confirm the efficacy of medicine (Gyawali et al., 2017).

Data privacy

Data privacy regulation can be a hurdle in terms of working with RWD

Society has gathered masses of data, but unfortunately not all data are available for analysis. This is especially due to privacy concerns. There are ethical concerns among doctors about whether they are allowed to disclose patient data. Moreover, medical data protection is a major concern for the public and European regulations (Miani et al., 2015). Thus, even though technological developments allow

for RWD to potentially provide great advantages, some data extractions are simply not allowed by the law. Patients participate in RCT under informed consent. Therefore, RCT does not face the same data privacy issues as with the usage of RWD (Armitage et al., 2008).

8.4.3.2 Considerations while applying

Degree of control

RWE can be more difficult to influence as it is conducted post data collection

Data collection and the analysis of data within RWD happens after the data are obtained for the original purpose. Therefore, RWD can utilize databases which already exist. RCT data are collected and analyzed on an ongoing basis. Hence, it is more difficult to influence the treatment in RWD compared to RCT (Gyawali et al., 2017).

Sample size

RCT requires resources to control substantial but limited sample sizes, whereas RWD can have very large sample sizes utilizing existing data sources

RCT requires substantial amounts of patients to identify difference between treatments, making it costly and complex to manage. However, when comparing RCT and RWD, RWD's sample size can be substantially larger than RCT. This is due to the fact that RWD can utilize pre-existing patient data derived from atypical sources like insurance claims, disease databases, and pharmacy data bases. Assuming that data preparation has been conducted for RWD, then RWD would be less costly to work with even though the sample size could potentially be much larger (Gyawali et al., 2017).

Population

RCT can be subject to selection bias, but RWE can give insights on untraditional populations

The patient population in RCT is well defined within the constraints of specific eligibility criteria where the obtained results reflect the outcomes in the limited population. The controlled environment also offers more internal validity (e.g. patients will take the right amount of medicine at the right time, which is not always the case in the real world). However, RCT has been subject to criticism as well. The controlled and defined population can be subject to inherent selection bias. Studies have shown that fewer than 5% of adult cancer patients participate in clinical trials, and those patients that do participate are often healthier, younger, and less diverse compared to their real-world counterparts (Sherman et al., 2016; Gyawali et al., 2017; Makady et al., 2018). Hence, results obtained from RCT

does not necessarily reflect the real world. This is where RWE can have its advantages. RWE is from the real world and can reflect the real world to a higher degree, where patients do forget to take their medicines. At the same time, RWE can encourage evaluations of the patient population which is not normally studied in clinical trials, thereby offering new insights on patients and potentially helping medicine expands its indications [11]. Indication expansion could also provide pharmaceutical companies additional revenue sources (Gyawali et al., 2017; Samuelsen, pers. comm., March 22, 2018).

8.4.3.3 Outcome considerations

Bias risk and toxicity

RCT minimizes the risk for data bias and confounding, but RWE can help uncover previously unknown long-term toxicity signals

One of the biggest advantages of RCT is its randomization in which blinding is possible. This minimizes the risk for data bias and confounding. RWE does not have the same possibility for blinding and randomization and can therefore lead to higher chances of bias and residual confounding. However, RWE might help uncover important toxicity signals that need long-term follow-up analyses. The probability of important toxicity discoveries would be much lower in the case of RCT where only acute and common toxicities are usually found (Gyawali et al., 2017). Additionally, RWE may not be as effective in isolating the "real" effect of a medicine e.g. if a patient in the real-world takes multiple medications, it would be difficult to isolate the effect from the medicine which is investigated (Sherman et al., 2016).

Therapy approval - RWD to support or replace?

RCT is the main method for medicine approval, however RWD could support or partially substitute RCT with the use of big data

Regarding the approval of medicine, RCT is the current gold standard (Gyawali et al., 2017). RCT is much more controlled in comparison to RWD and the population chosen is often stronger and healthier relative in the real world. Patients also voluntarily participate, well aware of the risks related to participating in clinical trials. Hence, it can be justified that new medicines can be tested on these patients. RWE might not be suitable to the same extent with current technology to approve new

[11] A sign or circumstance that points to or shows the cause, treatment, or some other aspect of a disease (Medical Dictionary, n.d.)

medicines, as the risk related would be too high. Selling untested medicines without RCT could have fatal consequences. Gyawali et al. (2017) argues that RWE should support RCT rather than be used for medicine approval. However, Rassen (2017) argues that RWD could substitute certain RCTs. In one instance, an RWD platform generated RWE where there was no compromise on quality and the "time to evidence" was accelerated. The RWD analysis was completed before the RCT analysis with the same question and had analogous results (Rassen, 2017). The RWD analysis had 9,218 patients from a wide variety of clinical settings while RCT enrolled 1,538 patients. Given the vast flow of big data and the technology advancements pertaining to data analytics, it may not be optimal to solely rely on RCT for health technology appraisals and medicine approval. Combining big data with the right science could provide high-quality evidence to support decision making (Ibid.).

8.4.4 Sub-conclusion

Whether it is best to use RWD or RCT is a difficult question, and it can be difficult to conclude that one measure is better than the other. RWD can reflect the real world and real patients to a higher degree, but the results can vary depending on the data quality. RCT is currently the gold standard, but it is still far from perfect. It is costly and fails to mimic the real world to the same degree as RWD. However, it can be useful to apply both RWD and RCT in a health technology appraisal if both tools are applied carefully in order to combine their respective strengths and avoid significant weaknesses. From the assessment, relying primarily on RCT is still worthwhile, but using RWD and RWE to support the health technology appraisal could yield more optimal results. The comparison between RWD and RCT can be seen in Table 8.2.

Table 8.2: comparison of real-world data and randomized controlled trial

Category	Real-world data	Randomized controlled trial
Considerations before applying		
Controlled vs. real-world	• Reflects the real-world • Not artificial environment • External validity	• Gold standard • Premarket evaluation • Internal validity
Application costs	• Low incremental costs • High initial costs (reliant on data quality)	• Costly
Data quality	• Data not standardized • Lack of data sharing • Methodological challenges • Statistical validity is questionable • Proxies and assumptions must be made	• More controlled data • Utility measure (QoL) questionable
Data privacy	• Privacy concerns and data regulation	• Lower degree of privacy concerns
Considerations while applying		
Degree of control	• Difficult to influence data	• Easier to influence data
Sample size	• Potential very big sample size (big data) • Utilize existing data	• Limited samples size; prior knowledge required for sample size calculation
Population	• Evaluation non-traditional population • Data from atypical sources	• Defined population within constrains • Inherent selection bias
Outcome considerations		
Bias risk and toxicity	• True randomization and blinding not possible • Data bias and residual confounding • Issues in terms of isolating "real" effect of medicine • Can reveal toxicity signals, requiring long follow-up • Facilitate post marketing surveillance	• Possible to have true randomization and blinding • Minimize risk for data bias and confounding • Only reveals acute, common toxicities • Clinical equipoise can be lost when strong signs are available from real world or early-phase clinical trials
Therapy approval	• Verify evidence in the real world • Indication expansion for medicines • Shorter time to answer	• Considered the gold standard necessary for new drug approval

Source: table by authors (2018) based on chapter findings

8.5 Risk-sharing agreements

This section introduces the concept of risk-sharing agreements ("RSA") within VBP. RSA is not a pricing model, but an agreement under which VBP is applied. RSA has gained popularity in health economics (Mahjoub et al., 2014). This is due to the price increase in numerous new medicines such as cancer drugs and biopharmaceuticals becoming more expensive (Walker et al., 2012). However,

the effectiveness outside the clinical trials are often uncertain at market approval, thus making it difficult to decide whether to reimburse medicine. In addition, the evidence available at a medicine's launch is mainly focused on the regulator's needs and not on the needs of the purchaser's decision making. Hence, there is often little material on relative effectiveness in routine use or against existing interventions. Information on relative cost-effectiveness is also severely lacking. This leads to cases with substantial ambiguity surrounding the consequences of these medicines' widespread use (Ibid.).

8.5.1 What are risk-sharing agreements?

According to WHO, risk-sharing agreement is defined as *"A contract between two parties who agree to engage in a transaction in which there are uncertainties concerning its final value. Nevertheless, one party, the company, has sufficient confidence in its claims of either effectiveness or efficiency that it is ready to accept a reward or a penalty depending on the observed performance of its product.*" (Vogler and Zimmerman, 2016, p. 107). By definition, an RSA is similar to "a money back" guarantee in consumer products, which gives the perception of confidence and quality (Schoonveld, 2015).

RSAs are mostly applied to new medicines where there is little evidence or unproven long-term health benefits (Schoonveld, 2015). In practice, the agreement is about setting the frame and realizing the shared responsibilities between both companies and payers in regard to the "risk". The "risk" depends on the situation and can result in higher than expected increases in pharmaceutical spending or lower than expected health gains (Adamski et al., 2010). The paper is aware that different types of RSA exists. Their common characteristic is that they enable patients to get access to new medicines which would otherwise not be available at the time of the product launch (Piatkiewicz et al., 2017). However, these will not be further elaborated on as the focus is to investigate the nature of RSA and VBP.

8.5.2 Risk-sharing agreements – benefits and challenges

RSAs can remove the financial incentives for companies to deliver unnecessary services that exist when compared to the direct purchase of medicine (Table 8.3 shows an overview of benefits and challenges). This is because the payers' objectives can be clearly defined in such an agreement (Guy D'Andrea, 1994). However, it requires a clear definition of what is expected from the medicines, and in some cases, this can be difficult. In cases of weak evidence, the payers might argue that medicines did not deliver expected outcomes, whereas the supplier will argue the opposite. At the end, if the company is unsatisfied with the outcome a case can end up as a lawsuit in which the decision is ultimately left to the court. This can often be expensive for both parties. As Kjellberg pointed out in an interview, even though RSAs can seem theoretically sound, in practice it might be difficult to pull

off due to potential lawsuits and administrative costs. This indicates that the cost of implementing RSAs can be higher than the actual gain obtained (Kjellberg, pers. comm., April 4, 2018), this is further supported by Adamski et al. (2010).

RSAs are also said to be able to limit the growth in pharmaceutical expenditures while ensuring that the health gain is maximized within the limited budget (Adamski et al., 2010). Additionally, RSAs can also create medicine access to patients. Medicines which are deemed too expensive relative its proven value at product launch, can be offered to patients through RSAs, allowing patient access (Mahjoub et al., 2014). Companies can enjoy the extra data generated through the new patients, which it can use in the future to prove its medicine's efficacy and effectiveness (Schoonveld, 2015). Thus, it can also address issues such as the safety of the products in practice (Adamski et al., 2010).

Walker et al. (2012) also point out that even though patients get early access to the technology, RSAs may reduce the likelihood of pharmaceutical companies investing in additional research once the product is covered, thereby reducing the likelihood of additional health gains for future patients. Furthermore, payers might also be paying for cost ineffective technologies (Ibid.).

Table 8.3: risk-sharing agreements – benefits and challenges

Benefits	Challenges
• Removes financial incentives for unnecessary services • Can limit growth in pharmaceutical expenditure • Accelerates patient access to medicine • Additional early market data generation for companies	• Needs clear definition of treatment outcome • Ambiguous results lead to high additional costs • High administrative costs • Reduces likelihood of additional research on approved medicine

Source: table by authors (2018) based on chapter findings

From the benefits and challenges, conditions in which RSAs can be considered have been identified:

1) Limited budget with increasing expenditure on medicine or a desire to containing costs
2) Evidence on efficacy of medicine is ambiguous or limited, thus requiring further testing to benefit both payers and sellers through additional data
3) Establishments of clear definition on failure and success to avoid ambiguity in RSAs
4) Low administrative costs related to the RSA so that it does not outweigh the benefits

In conclusion, there has been a need for RSAs due to the rising prices within medicines. They can provide benefits to create disincentives for unnecessary health services, limit expenditures, give

patient access to medicine, and provide companies with medicinal data. However, RSAs should be used wisely in situations where the optimal conditions are met, and only if costs can be managed.

8.6 Case study on England and value-based pricing

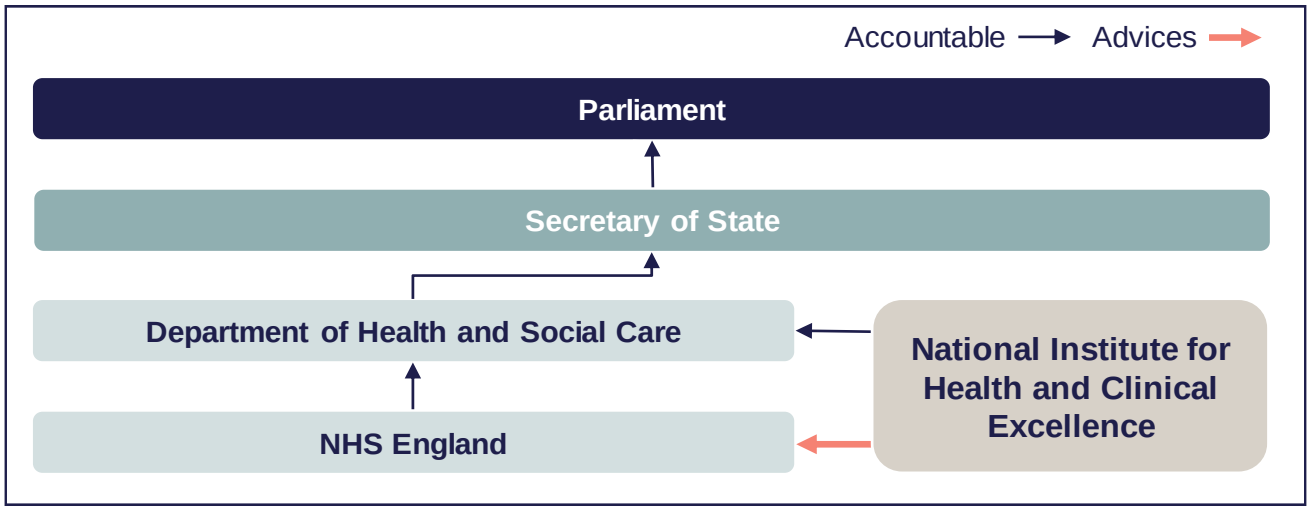
England has been chosen as a case study because the country has been working with VBP through the *National Institute for Health and Clinical Excellence* ("NICE") since 1999. Therefore, it has built up years of experience within the field (ABPI, 2018). Although the described system applies throughout the UK, this paper will limit the scope to focus on England.

The following section will give a short introduction of the most important institutions in terms of medicines pricing in England. The focus will be on the application of VBP within NICE.

8.6.1 Healthcare system in England

The National Health Service ("NHS") is the public health services in England. The structure of NHS (see figure 8.4) mainly consists of: The *Department of Health and Social Care* and the *Secretary of State for Health*, both of which are ultimately responsible for the health system as a whole. The *Clinical Commissioning Groups* ensures that the objectives, set out in an annual mandate by the Secretary of State for Health, are met. NICE sets out guidelines for clinically effective treatments and appraises new health technologies for their efficacy and cost-effectiveness (Ibid.).

Figure 8.4: main institutions of the English Public Health Care system



Source: own illustration based on Thorlby, Aora and Trust (2017); NICE (2018). Note: only relevant institutions included

8.6.2 Medicine pricing in England

NHS is the main buyer of pharmaceutical products in England. The pricing of branded pharmaceutical products is under the regulation of the *Pharmaceutical Price Regulation Scheme* ("PPRS") and the

Statutory Scheme, whereas generic medicines are priced freely (to a certain extent). Therefore, there are no direct negotiations between the government and the companies apart from when the schemes agreements are made (Chalkidou, pers. comm., April 25, 2018).

8.6.2.1 Pricing of branded medicines

This section will briefly cover PPRS with an emphasis on how PPRS affects pricing. However, this section will not go in depth into PPRS, as Section 9.4 will cover the topic to a further extent to illustrate how PPRS is used as a tool for profit control.

The PPRS is a voluntary agreement between the Department of Health and Social Care and the *Association of the British Pharmaceutical Industry* ("ABPI"), which is renegotiated approximately every five years. PPRS' role in medicine pricing is to set controls on the prices of branded medicines sold to the NHS, which covers all licensed branded, prescription medicines. PPRS does not cover generic medicines nor over-the-counter ("OTC") medicines, except when prescribed. For companies that are not a part of the PPRS agreement, the jurisdiction falls under the Statutory Scheme (Ranson, 2017). Therefore, pharmaceutical companies are able to set their own prices, so long as it follows the limits of the PPRS agreement and NICE guidelines.

The statutory scheme is imposed on companies that are not voluntarily a part of the PPRS agreement. Under the statutory scheme, companies had to apply a one-time 15% reduction to the maximum branded medicines' selling prices on December 2013 (Ranson, 2017; The Pharmacist, 2018). Similar measures are implemented for medicines introduced after this date. In the beginning of 2018, the government has planned to replace the price-cut mechanism. This includes a payment system where companies that have chosen the statutory scheme will pay 7.8% of their net NHS sales to the Department of Health and Social Care. This change will also limit the maximum price that a company may charge (The Pharmacist, 2018). The scheme also provides the right to appeal against "enforcement decisions" as well as price limits set by the Secretary of State (Ranson, 2017).

8.6.2.2 Pricing of generic medicines

The main factor that drives prices down for generic medicines is competition. This is also reflected in the prices paid by the NHS for generic medicines, as generic medicines under the Drug Tariff are mostly set by reference to the market prices (Tillett et al., 2017). Traditionally, generic pricing of medicines has been kept low due to the competition. However, around the year 2017, there was increased attention from the media and government on cases where generic suppliers have "peaked" the prices of older generic medicines in situations of lower market competition (Tillett and Arnold,

2017; Tillett et al., 2017). As a response, the Government imposed legislation which enabled the Secretary of State to limit prices of unbranded generic medicines. This served as a method to prevent a "loophole" which the government was previously unable to control (Ibid.).

8.6.3 NICE and its health technology appraisal

The English NICE is an important institution for understanding how VBP is used in practice. Through its health technology appraisal, NICE ascribes value to new treatments (UK Department of Health, 2014). This section will provide an understanding of NICE and discuss its methodology.

Since 2000, NICE has published guidance on health technologies such as medicine and medical devices. In 2005, they began publishing public health interventions and in 2013, the organization also began developing social care guidance (George, 2016).

NICE guidance is based on value assessment using published clinical and cost effectiveness criteria for decision making. The assessment applies the perspective of the entire NHS system, and is defined through an assumed opportunity cost – adopting a new medicine displaces health benefits elsewhere in the NHS (George, 2016). The rationale behind NICE's technology appraisals and methods comes from the reality of a fixed NHS budget constraint (Claxton et al, 2011). To ensure consistency and fairness across all therapeutic assessments, NICE uses the measure of quality-adjusted life years ("QALY") to value treatments (George, 2016). Any medicines recommended through NICE's technology appraisal must be funded by the NHS and be available to patients with valid prescriptions, within 90 days (George, 2016; Ogden, 2017; Quinn, 2017). Hence, NICE recommendations are the main source of guidance for new medicines within the NHS. As such, the NICE recommendations are meant to standardize healthcare access across the country, to ensure equal access to medicines (Ibid.). However, NICE realizes that there are differences with respect to end of life treatments compared to non-life-threatening treatments, and hence NICE ascribes certain diseases or populations with different QALY multipliers (Chalkidou, pers. comm., April 25, 2018).

8.6.4 Using QALY to measure effectiveness

The next question to pose is how NICE ascribes value to life, health, and wellbeing. The main measure used is QALY (Ogden, 2017). QALY is used in cost-utility analysis as the measure of health benefits of treatments. QALY to enables consistency and fairness across all decisions (George, 2016).

Table 8.3: example of QALY calculations

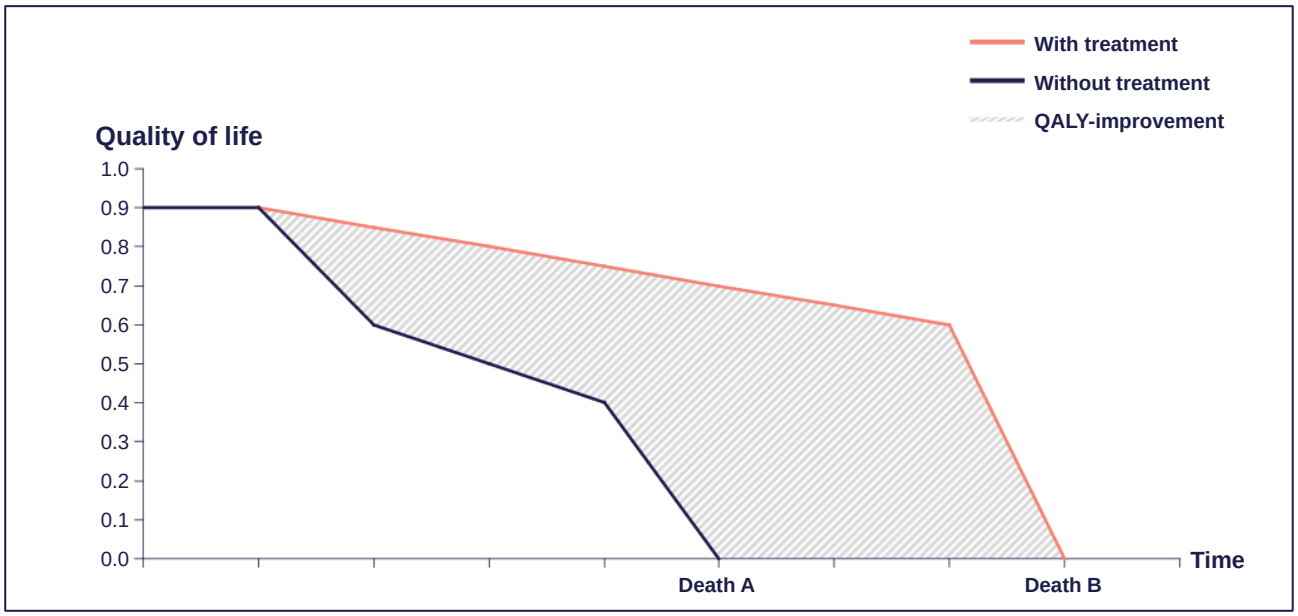
Patient example	QALY calculation
Perfect health for 1 year will have:	1 year of life x 1 utility value (QoL) = 1 QALY
Perfect health for 0.5 year will have:	0.5 years of life x 1 utility value = 0.5 QALY
Patient with utility value: 0.5 (half perfect health) 1 year:	1 year of life x 0.5 utility value = 0.5 QALY

Source: table by authors (2018) based on Ogden (2017)

QALY assesses the effect of a given treatment by multiplying the length of life with an index measuring quality of life ("QoL") (see Table 8.4). QALYs are assigned a value between 0 – 1. One year of perfect health is given a value of 1 QALY, one year with less than perfect health is given a value of QALY between 0 – 1, and patient death is given a value of 0 (Ogden, 2017).

QoL is measured based on NICE's definition which combines a person's overall physical, mental, and social well-being. A patient's QoL is assessed through a questionnaire where the questionnaire answers are converted into utility values from 0 – 1. The measure can be retrieved from clinical trials as these QoL surveys are a standard part of clinical trials. After receiving the QoL measures, NICE converts the benefits of the treatment into QALYs (Ogden, 2017). Figure 8.5 is an illustration of how QALY is combining both quality of life and quantity into one single index value. The figure visualizes the expected quality of life improvements that a treatment will offer over time (Pettitt, 2016).

Figure 8.5: Illustration of QALY



Source: figure by authors (2018) based on Pettitt (2016)

In conclusion, the cost effectiveness of a new treatment is expressed as cost per QALY gained compared with standard care, which can also be defined as the incremental cost per QALY gained. NICE does not have threshold in which interventions should or should not be recommended. However, in general, NICE considers treatments costing less than 20,000 GBP per QALY gained as cost effective. Treatments costing between 20,000 - 30,000 GBP per QALY gained might also be considered cost effective, given that certain conditions are satisfied. Nevertheless, this does not mean that NICE rejects treatments above 30,000 GBP per QALY. The organization does not reach a conclusion based on cost effectiveness grounds alone (Ogden, 2017, NICE 2018).

NICE also accounts for the following factors: the degree of certainty and misrepresentations in health gains. The degree of certainty around the incremental cost effectiveness ratio requires advisory bodies to be more cautious when recommending a technology in situations where they are less certain about the incremental cost effectiveness ratio presented in the cost effectiveness analysis. In regard to misrepresentation in health gains, there may be strong reasons indicating that the assessment of the change in the QoL is inadequately captured. This may occur when the intervention is an innovation that adds demonstrable and distinct benefits that are not adequately represented in the measurement of health gain. Additionally, NICE must also include other factors when developing its guidance, e.g. the need to distribute health resources in the fairest way within the society (NICE, 2008; Ogden, 2017; NICE 2018). Professor Chalkidou, a health economics professor from Imperial College, adds that NICE has certain multipliers it will use for certain patient groups. For example, end-of life treatments often have multipliers, which increases willingness to pay (Chalkidou, pers. comm., April 25, 2018).

8.6.5 QALY – benefits and challenges

QALY's main advantage are (see Table 8.5):

1) *QALY is a single metric to measure health outcomes and helps to simplify the complexity of measuring health outcomes.* With one single metric, QALY is able to combine the effects of health interventions on mortality and illness (Pettitt et al., 2016).

2) *QALY facilitates comparisons of health outcomes across diseases*. QALY makes it possible to compare health improvements and outcomes across treatments and diseases. This is important in health technology appraisals as the goal is to efficiently allocate budgets, often constrained, across different diseases. Hence, a comparable measure is needed and QALY provides a "common currency" solution to enable this (Devlin and Lorgerly, 2017; Pettitt et al., 2016).

3) *QALY offers consistency.* The consistency obtained can ease the process of prioritizing medicines against each other (Ogden, 2017; NICE, 2018).

4) *QALY allows optimization of resource allocation via rational and explicit methodologies.* QALY allows for a scientific evidence-based approach to measure cost effectiveness (Pettitt et al., 2016).

5) *QALY can offer more transparency*. For institutions that are conducting health technology appraisals without any measure, QALY can offer more transparency. The transparency can make it easier for the public to understand, thus easier to justify health technology appraisal decisions (Goldman, pers. comm., April 4, 2018).

Disadvantages related to using QALY can be divided into three groups: methodological issues and theoretical challenges, ethical considerations, and context or disease specific considerations.

Methodological and theoretical challenges

Measuring and deriving QALY can also pose certain challenges (see Table 8.5):

1) *Variation in measurement techniques and methods*. Scholars have argued that valuation of utility and well-being are often developed with small, non-representative sample sizes (Pettitt et al., 2016).

2) *Validity and reliability of measurement concerning utility value of health.* Several authors have also expressed concerns in terms of the reliability and validity of measurements focused on utility value of health state. For example, it was found that study participants would sometimes misunderstand the utility scale used in these measurements (Ibid). Different populations can also evaluate health conditions differently – e.g. utility value derived from RCT participants compared to the general public might not be the same (Pettitt et al., 2016; Makady et al, 2018).

3) *Utility scores do not account for contextual factors*. Utility scores do not account for factors such as prevalence of disease, initial health state, or caregiver status, etc. The beneficial externalities are therefore not captured in the same QALY calculation (Ibid.).

4) *Utility scores do not account for time and population preferences*. During different economic or social times, a population might value some medicines higher than others. Likewise, medicines might also be valued more in certain countries when compared to other countries. Diverse populations can have different demands which QALY does not consider (Kind et al, 2009; Pettitt et al., 2016.).

5) *Does not recognize non-health benefits*. QALY does not account for non-health benefits that can be considered important from a societal perspective. Examples include societal benefits from being a caregiver, faster return to work, and increased school performance. (Pettitt et al., 2016.)

Ethical considerations

Some of the ethical considerations that QALY gives rise to are:

1) *Can one life be valued over another?* The first criticism surrounds the valuation of an individual's life over another's, as critics argue that perfect health does not necessarily make life more or less valuable (Pettitt et al, 2016).

2) *How to determine personhood?* To measure quality of life, life must be present. However, in the case of fetuses and brain-dead patients, it is debated if life fundamentally exists (Ibid.).

3) *May set false limits on healthcare.* QALY can be used to rationalize overly restricted healthcare budgets, but it does not encourage improved efficiency or budget increases (Ibid).

4) *Potentially reduces freedom of choice*. In the same way it can set limits on healthcare, QALY's tendency of being more prescriptive of the available healthcare options reduces the freedom of choice and eventually, autonomous patient decisions (Ibid).

5) *Creates an overly utilitarian measurement methodology*. The quantitative QALY gives a very utilitarian approach which does not always offer the best outcomes. The fact that all QALYs are considered equal regardless of situational or patient factors have been criticized (Ibid.).

Context or disease specific considerations

1) *QALY does not consider disease specific or context specific considerations*. For example, whether it is palliative care, mental health etc. Hence, QALY does not consider the nuances required within disease groups and patients (Whitehead and Ali, 2010; Pettitt et al., 2016).

2) *QALY has insufficient sensitivity*. There is a lack of dimension when only using QALY as it does not fully account for patient situation. Patients with low endurance levels or those undergoing end-of-life treatments may have higher insensitivities to improvements in health status. This also applies to elderly populations as their age may hinder improvements in their health status (Pettitt et al., 2016).

3) *QALY reduces the role of experts*. There is a concern regarding the reduction in provider input. QALY has been criticized for reducing the healthcare provider's role and expertise as it undermines their ability to make decisions based on individual need (Pettitt et al., 2016).

From the above analysis of benefits and challenges of QALY, there are three identified conditions which are relevant to consider when applying QALY:

1) A need to measure cost effectiveness for health technology appraisal
2) A desire to compare different treatments and disease group consistently through one measure
3) An understanding that additional dimensions need to be considered in order to create an effective measurement

In conclusion, QALY is a measure of cost effectiveness which can simplify a complex health technology appraisal, offer comparison across treatments, give transparency, and help allocate resources in accordance with VBP. However, it can be difficult to use QALY as a stand-alone consideration if a complete technology appraisal is to be conducted because it does not encompass various ethical and situational factors. If QALY is to be applied effectively, the methodological challenges, ethical challenges, and context/disease specific considerations all need to be considered.

Table 8.5: QALY – benefits and challenges

Benefits	Challenges
• A single metric to measure health outcomes, and helps standardize the complexity of measuring health outcomes • Facilitates comparisons of health outcomes across diseases • Offers consistency • Allows optimization of resource allocation via rational and explicit methodologies • Enables transparency	**Methodological challenges:** • Variation in techniques and methods • Measurement validity in utility value of health • Utility scores do not account for contextual factors • Does not consider time and population preferences • Does not recognize non-health benefits **Ethical considerations:** • Can one life be valued over another? • How to determine personhood? • May set false limits on healthcare • Potentially reduces freedom of choice • Overly utilitarian measure **Context or disease specific considerations:** • Does not consider disease specific or context specific considerations • Has insufficient sensitivity • QALY reduces the role of experts

Source: table by authors (2018) based on chapter findings

8.7 Conclusion on value-based pricing

As a pricing model that considers both buyers and companies, VBP is seen by many influential stakeholders, such as governmental bodies, as a promising alternative to outdated pricing schemes. VBP is a tool to price medicines in a "fair" way while simultaneously encouraging innovation through which patients can derive great benefits. However, the main challenge of VBP is to derive the optimal methodology to measure value accurately from the most relevant data sources. Additionally, VBP is less valuable for pricing generic medicines, as generic medicines cannot contribute to innovation.

VBP also gives the opportunity to utilize randomized controlled trials and real-world data, both of which are important tools that provide insightful patient information. Through the use of both randomized clinical trials and real-world data, it is possible to achieve a new gold standard where controlled and uncontrolled outcomes are factored in to achieve more accurate insights in patient data. This will ultimately allow for the optimal derivation of value measurement for VBP.

Risk-sharing agreements have also become popular as a way of conducting VBP. It is especially effective in cases where a medicine is expensive and the evidence on its efficacy is ambiguous or very limited. However, its biggest challenge is the potential heavy administrative cost that comes along with the in-practice application. If it is possible to manage the costs of applying risk-sharing agreements, it could be considered a highly useful tool in VBPs.

Large public institutions such as NICE uses QALY, which is a cost-effective measure praised by many. It simplifies the complexities of health technology appraisals and combines several factors into one measure, therefore allowing for comparison across treatments and diseases. However, QALY is just a measure and it fails to account for all dimensions of a health technology appraisal. Incorporating methodological challenges, ethical challenges, and context/disease specific challenges could provide a more holistic measurement.

Ultimately, VBP is a valuable tool with many great benefits. However, it should be applied carefully and with the knowledge of its strength and limitations.

9 Profit control

9.1 Introduction

The pharmaceutical industry has historically been highly profitable, having the highest return on invested capital among all industries between 1995 – 2004. In 2013, the pharmaceutical company Pfizer had a profit margin as high as 42% (Wagstaff, n.d.; Jiang and Koller, 2006; Chen, 2015) Additionally, this paper notes that medicine manufacturing is generally inexpensive, as the incremental cost of producing small-molecule medicines can be quite low (Danzon and Towse, 2003; Price II, 2014). Hence, this has given rise to the question of whether the prices charged by pharmaceutical companies are too high (LaMattina, 2018). These high profits have lead politicians to implement profit control policies, where limits are put pharmaceuticals' profit margins (Łanda et al., 2009).

9.2 What is profit control?

WHO describes the following on profit control: *"A profit framework is negotiated periodically between the state and the pharmaceutical industry. This framework is fixed for each individual manufacturer. Within this framework manufacturers are free to set their medicine prices […]"* (Vogler and Zimmerman, 2016, p. 97). Hence, profit control is an agreement which limits the profit from sales of medicines. Companies are free to set prices, as long as it does not exceed the profit limit. If it does, the additional profit must be returned. Ultimately, the purpose is to control medicine expenditures (Łanda et al., 2009).

9.3 Profit control – benefits and challenges

An overview of benefits and challenges of profit control can be found in Table 9.1.

Some of the benefits of profit control are:

1) *Easy to communicate*; the idea of profit control is simple to describe and is easily understood by the public.

2) *Give the feeling of "fairness"*; profit control can give the feeling of fairness for both payers and sellers. As profit control considers that pharmaceutical companies should make some profit, however not excessive amounts of profit, which exceeds payers' limits. Hence, the theoretical idea of profit control considers the interests of both payers and sellers.

3) *Avoid extreme price gouging*; profit control can set a limit for pharmaceutical companies. Hence, an extreme high price can be avoided for payers (Łanda et al., 2009).

Although, the principle of profit control may sound simple, there are challenges related to profit control as well.

1) *Bureaucratic and costly to administrate*; for profit control to work, the annual financial review needs to be conducted for all the companies within the agreement. Companies must deliver quarterly sales reports, company declarations, unaudited and audited annual sales reports, etc. (Barham, 2017). Therefore, the process of conducting profit control requires significant resources.

2) *Not taking the interest of pharmaceutical companies*; pharmaceutical companies' profits are dependent on its products and pipeline. At times, these companies may be very successful with many innovative medicines being marketed in a row. At other times, they may have a less successful period with no new medicines. Developing a new medicine can take more than 10 years, and it is far from all R&D investment that results in marketable medicines (Danzon and Towse, 2003). Hence, it can be argued that companies should not have profit limits, as successful periods are required to make up for the less successful periods (Torjesen, 2015). Thus, it can be questioned whether it is justified that pharmaceutical companies should have limits on profits.

3) *Price do not necessarily reflect value*; as the companies can set prices as they wish, as long as it does not exceed the agreed limit, there is no guarantee that prices obtained through profit control actually reflects the healthcare value that the patient receives (Łanda et al., 2009).

4) *Creates the wrong incentives.* Profit control can create lower incentives for companies to reduce costs. The rationale behind is that lowered cost would lead to lowered prices, leaving the company with the same profit (Cabral, 2000).

Table 9.1: profit control – benefits and challenges

Benefits	Challenges
• Easy to communicate • Is perceived as fair • Prevents extreme price gouging	• Bureaucratic and costly to administrate • Not considering up and down periods • Price does not necessarily reflect value • Creates the wrong incentives

Source: table by authors (2018) based on chapter findings

Having covered the benefits and challenges, the following conditions should be considered when applying profit control:

1) Limited budget with increasing medicine expenditure
2) A need for a measure which is simple and easy for the public to understand
3) A need to avoid extreme price gouging
4) It is evaluated that the cost of administration does not exceed the benefits gained

9.4 Case study – the Pharmaceutical Price Regulation Scheme in England

This section presents England's PPRS as it is known as the most prominent example of profit control (Seget, 2005). As England's healthcare system has already been outlined in Section 8.6, this will not be covered again. PPRS was briefly introduced in Part 8.6.2, this section will go through PPRS in detail with a focus on how PPRS works as a profit control tool.

9.4.1 About the Pharmaceutical Price Regulation Scheme

The UK introduced profit control in 1957 through PPRS. The PPRS is a voluntary agreement between the UK Government, represented by the Department of Health and Social Care and the Association of the British Pharmaceutical Industry (ABPI). Normally, the PPRS agreements are negotiated every five years. However, it has often lasted for more than five years and has only once been terminated earlier. Hence, it gives both the government and the industry stability and predictability, enabling both to plan ahead (ABPI, 2014).

According to the agreement, companies may freely set prices of agreed products, as long as the profit limit is not exceeded. If the profit limit is exceeded, the company is obligated to lower medicine prices on products of its own choosing, or to return excess profits (Ibid.). PPRS does not guarantee profits and the profit limit is based on a range of maximum allowances covering R&D costs, information, sales and marketing, and general administrative costs. These are then subject to a maximum percentage profit. (ABPI, 2014). PPRS does not stand alone in this process, as NICE's health technology appraisal is a part of pricing medicines as well. Before a product can be reimbursed, it needs to be assessed by NICE. NICE will determine whether or not it is cost effective. If NICE decides it is cost effective, the product will be subject to reimbursement (Ibid.).

In 2014, new features were introduced to PPRS. Related to profit control specifically was a framework to determine reasonable limits to profits from branded medicines to the NHS. There were two limits: 1) allowable "Return on Capital" target on 21%. The target is based on the historical value of average capital employed. 2) The margin of tolerance has been increased to 50% from the previous 40% (Ranson, 2017). This indicates that, if a member's profit exceeds the 21% target by more than 50%, there will be demanded a repay of the excess profit, or a reduction of prices by equivalent

amount. In case, a member's profit is above 50% but below 21% target, then the member will be allowed to apply for a price increase (Ibid.).

Other features introduced in the PPRS 2014 included (Barham, 2015; Ranson, 2017): 1) Annual financial review is required for members with >50 million GBP sales to the NHS. 2) Patient Access Scheme was introduced, aiming at facilitating patient access to medicine where NHS with current evidence base is unlikely to support the list price. 3) Corporations are allowed to adjust medicine prices, as long as the overall effect on the company's whole portfolio is neutral. 4) New active substances may be priced in the discretion of PPRS members, on market entry. However, the price is expected to be close to NICE assessed value.

9.4.2 Pharmaceutical Price Regulation Scheme – benefits and challenges

The topic of whether PPRS should be phased out or remain in place has been discussed extensively. The result of the discussions ended in 2014, as PPRS 2014 was implemented. Even though the government planned on continuing with value-based price ("VBP") only, this was not favored by the industry (McConaghie, 2014). Thus, it is interesting to assess PPRS and whether it is beneficial or not. An overview of benefits and challenges can be found in Table 9.2.

Table 9.2: PPRS – benefits and challenges

Benefits	Challenges
• Favors quick introduction of medicines • Provides stability and predictability	• Unscheduled changes • Historically not successful at cost containment • Damaging to small medium-sized companies • Companies are not obligated to supply • Some companies choose the Statutory Scheme

Source: table by authors (2018) based on chapter findings

One of the claimed advantages of PPRS is its ability to enable quick introduction of new medicines into the healthcare system (Łanda et al., 2009). This is correct to some degree. The companies can set prices "freely" within the agreed limit. However, before a medicine can be reimbursed by NHS, it has to go through NICE's health technology appraisal and be declared recommended. This process can take up to 54 weeks (Drummond, 2009). Therefore, compared to a direct negotiation process between NHS and the respective companies, PPRS might allow a quicker introduction of new medicines. However, in practice health technology appraisal process can delay access (McKee, 2017).

One of the objective of PPRS was to give stability and predictability of regulation (ABPI, 2018). Indeed, the five-year length of the agreement could be considered a way to secure stability and

predictability. Hence, this could be one of the advantages of having predetermined profit control, with prearranged limits. However, this has been criticized by Barham (2017), who points out that PPRS has not been entirely stable. There have been some unscheduled changes made in PPRS 2014, e.g. amendments were made in August 2015, which had the effect of lowering PPRS payments. Barham (2017) also points out that even though PPRS has been predictable in many senses, it has been challenging for pharmaceutical companies. The government knew in advance how much NHS expenditures on branded medicines, sold by PPRS members, would be allowed grow. However, companies did not know how much expenditures would grow, and therefore how much they would have to pay back to stay within limits. Thus, even though PPRS offers some predictability, it is not fully living up to its first objective.

From a historical perspective, PPRS has not always had proven successfully in terms of cost containment. In the years between 1967 and 1997, the pharmaceutical budget increased at the mean annual rate of 10% (Łanda et al., 2009). It was at the same time criticized for its lack of transparency (Ibid.). In 2007, the Office of Fair Trading ("OTF") also published a report regarding profit control. The verdict was that profit control was detrimental to the system, and that changes should be made. It stated that much of the budget went to overpriced medicines. OTF found that prices of more than ten identified medicines were ten times higher than those of alternative medicines with similar therapeutic effects (Ibid.). Evidently, PPRS as a standalone mechanism does not offer any contribution in terms of cost savings nor VBP. However, having NICE as an institution, it can be argued that this issue is addressed to some degree if the entire medicine pricing system is viewed as a whole.

Additionally, one critic stated that PPRS is damaging to small medium sized enterprises ("SME"). McKee (2013) claims that SMEs are responsible for about 80% of innovation. However, 5 million GBP exemption threshold taper for companies with net sales between 5 million – 25 million GBP has been removed. Consequently, it means that companies with net sales below 5 million GBP in 2013 will pay no rebate on NHS sales in 2014, whereas companies with net sales of 5,000,001 GBP will have to pay 187,000 GBP to the Department of Health and Social Care the following year (McKee, 2013; McConaghie; 2014).

Critics have also criticized the degree of downward price modulation that is allowed, and are disappointed that it does not contain obligations to supply medicines. The downward price modulation is the freedom which is given to companies to increase or lower their medicine prices, as

long as it does not exceed the profit limits. The British Association of Pharmaceutical Wholesalers claims that the price modulation is used by companies in a more strategic way than previously. Some companies reduce prices of branded products with high parallel import competition, making parallel importation less economic and therefore eliminating the competition. However, companies that are lowering their prices are not obligated to supply the medicine, reducing patient access (McKee, 2013). However, it is important to understand that this is the perspective of parallel importers. Parallel import also has its disadvantages, which are discussed in Part 5.3.2.

Tillett and Arnold (2017) also concluded that PPRS 2014 has not been as successful as the Government had hoped in delivering savings to the NHS. This was partly due to companies choosing to move products out of PPRS into the alternative Statutory Scheme, which does not include back payments – hence lower savings for the NHS (Tillett and Arnold, 2017).

To sum up, PPRS seems to be effective at taking the perspectives of both payers and companies, offering some stability and predictability. However, PPRS is not solely based on profit control, as it includes elements from VBP through its patient access schemes. Therefore, profit control is not enough by itself to regulate medicine prices. Additionally, PPRS has historically not been able to stop increase in profits, and it did not achieve the savings NHS had hoped for. Unscheduled changes are also seen in PPRS, revoking some of the predictability from the scheme, and was seen as damaging for some SMEs. Thus, PPRS has is well-intentioned, but is burdened by some of its challenges.

9.5 Conclusion on profit control

In conclusion, profit control can theoretically have great benefits. It is simple to describe and easily understood, provides a feeling of fairness, and avoids extreme price gouging. Additionally, PPRS can also to some extent enable quick introduction of medicines and provide some predictability and stability. However, profit control can be very bureaucratic and costly to administrate, as financial reports need to be investigated continually. Prices under profit control do not necessarily reflect therapeutic value, which has historically lead to high prices of me-too medicines. Furthermore, it does not consider that companies can have highly variable profits over time due to changes in the life cycles of their medicines.

Thus, profit control should be used with caution and it is especially important that the cost of administration does not exceed the benefits created by profit control.

10 External Reference Pricing

10.1 Introduction

External reference pricing ("ERP") is widely used as a regulation tool by policy makers in Europe, with the purpose of containing medicine costs. ERP was applied for the first time in Canada in 1987. Subsequently, ERP has become the most widely used drug price control method in the OECD countries (Rémuzat et al., 2015). Hence, it is worth investigating the reasons behind the popularity of ERP.

10.2 What is external reference pricing?

According to WHO, ERP is defined as *"The practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country."* (Vogler and Zimmerman, 2016, p. 35).

The processes of ERP implementation and availability of price information varies from country to country (Rémuzat et al., 2015). Thus, ERP calculations also varies. In the study conducted by Rémuzat et al. (2015), it was found that 15 countries used the average price, 7 countries used the lowest price and 7 countries used other calculation methods. Hence, it is important to understand that ERP is a tool with basic principles, which can be applied in different ways to adapt to different countries (Ibid.). However, comparing the application of ERP across countries is not the focus of this paper, so this topic will not be addressed further.

10.2.1 External reference pricing – benefits and challenges

Most European countries use ERP as an integral part of their medicine pricing process, since it creates the basis for price negotiation of new, innovative medicines. However, not all countries are using ERP, e.g. Sweden and the United Kingdom ("UK") are not using ERP (Rémuzat et al., 2015; Panteli, et al., 2016). Hence, investigating the advantages and challenges of using ERP is relevant to understanding if and how ERP should be implemented.

Table 10.1: external reference pricing – benefits and challenges

Benefits	Challenges
• Simple and easy to perform • Easily understood by the public • Reassurance to the public of comparable prices • Can drive down cost	• Can be subject to model manipulation • Difficult to measure impact • Not all transaction prices are available • Unreliable sources can make the model invalid

Source: table based on chapter findings

There are 4 main benefits of ERP:

1) *Simple and easy to perform*. ERP benchmarking is quite simple, making it easier to perform relative to other pricing models, such as VBP, which can be complicated and open to manipulation (Łanda et al., 2009; Persson and Jönsson, 2015; Rémuzat et al, 2015).

2) *Easily understood by the public, which gives transparency*. As ERP is simple, it makes communication easy and creates a higher degree of transparency for the public (Ibid.).

3) *Reassurance to the public of comparable prices*. ERP provides reassurance for the general public that prices are not higher than in other, comparable countries, providing a sense of fairness (Ibid.).

4) *Can drive down cost*. ERP can be used to drive prices down and, at least in the short run, produce explicit cost savings (Ibid.).

Four main critiques are presented in existing literature, the main points of which are described below:

1) *Can be subject to model manipulation*. There is an opportunity for the pharmaceutical companies to manipulate the model, through strategic launch of new products in different markets (Persson and Jönsson, 2015; Rémuzat et al, 2015). More specifically, Persson and Jönsson (2015) note that ERP does not provide incentives for stakeholder to act in line with optimal (welfare maximizing) pricing. First, pharmaceutical companies are incentivized to delay or limit access to new innovative medicines in countries with small markets and/or a low income. This can have negative impact in terms of health loss. Second, all countries can lose welfare/health as ERP reduces the opportunities for differential pricing, i.e. utilizing the ability and willingness to pay differs between countries. Chapter 5 demonstrated that being unable to price discriminate across countries leads to lesser access to medicines in low-income countries, lower profits for pharmaceutical companies, and higher prices of medicines in high-income countries.

2) *Difficult to measure impact*. There is substantial overlap between countries that cross-reference. Hence, it remains challenging to estimate the direct impact of a price change's effect on reference prices across many countries (Ibid.).

3) *Not all transaction prices are available.* It can be difficult to gather information on transaction price on reference countries as it is not transparent across countries (Ibid.).

4) *Unreliable sources making the model invalid.* There is a lack of reliable sources on price information, price heterogeneity, exchange rate volatility and hidden discounts. Hence, not all prices

from other countries can be considered reliable, as there is limited transparency on pricing mechanisms (Ibid.). As an example, UK is one of the most referenced countries in Europe (Rémuzat, 2015), and since the UK has started using VBP, the discounts the NHS receives from the companies are disclosed. Consequently, the list prices now deviate from the transaction prices. Thus, Kjellberg, health economics professor, stated in the interview the list prices have become "useless" in reference pricing context (Kjellberg, pers. comm., April 4th, 2018). This was further supported by Harten and IJzerman (2017), who showed that different countries are given different discounts and that listed and actual medicine costs in Europe can differ up to 100% between countries. Furthermore, transaction prices may be as much as 30% lower than list prices (Harten and IJzerman, 2017).

In conclusion, ERP can be easy to perform and simple to understand. Used correctly, it can drive down costs and as it is simple to perform, the benchmarking can be less costly relative to using a VBP approach. However, ERP only seems to be work in the short run, and it can be subject to manipulation, which may decrease welfare. If transaction prices from reference countries are not easily accessible, it may be costly to collect the data, and the validity of the model can be questioned. Hence, ERP should be used carefully and considered under abovementioned conditions.

From the above it can be derived that ERP can be applied under the following conditions:

1) A wish to lower medicine prices based on reference countries' prices
2) Need simple easy to understand pricing model
3) Need simple and easy to perform pricing model
4) Desires to compare prices with reference countries
5) Have access to reference countries medicine prices transaction price, and not only list prices

10.3 Case study on Norway and external reference pricing

Norway uses ERP, making it an interesting case to study to learn about potential benefits and challenges of real-world implementation. Moreover, Norway and Denmark are similar countries in terms of size, demographics, and wealth, making it more realistic to assume that potential findings would work in Denmark (Nørregaard et al., 2012; Fransen, 2015). As the focus of this chapter is on understanding ERP systems, this section will not go into details on how Norway applies VBP or other medicine pricing models.

10.3.1 Healthcare system in Norway

This part will briefly cover the main institutions related to pricing medicines in Norway.

The *Norwegian Medicines Agency* (in Norwegian "*Legemiddelverket"*), decides what medicine to reimburse for outpatients. The agency also determines whether a new medicine should be covered by evaluating cost-effectiveness in comparison with existing treatments, and it determines maximum prices as well (Ibid.). An important player in the second level is *Hospital Procurement* (in Norwegian "Sykkehusinnkjøp"[12]), which is owned by *Regional Health Authorities in Norway*. It is responsible for coordinating national purchase deals on behalf of Regional Health Authorities. Hospital Procurement has primarily the procurement function, it also collaborates with Norwegian Medicine Agency in the negotiation process for new, expensive medicines and about bidding process (COWI, 2016; Lindahl, 2017).

10.3.2 Medicine pricing process in Norway

There is set an annual overall health budget by the central government. The municipalities and regional healthcare authorities are responsible for maintaining their budgets (Lindahl, 2017).

The Norwegian Medicine Agency sets the maximum pharmacy purchase price, through two pricing systems: ERP and a stepped price model (in Norwegian trinprismodel). ERP is applied to branded medicines where there is no competition from generic medicines and the stepped price model is applied to generic medicines (Ognøy and Festøy, 2015). The Norwegian Medicine Agency also conducts pharma-economic analysis to evaluate whether medicines should be reimbursed. However, as the focus of this section is on ERP, this will not be elaborated on further (Ibid.).

10.3.3 Application of external reference pricing in Norway

10.4.3.1 ERP and maximum prices

In Norway, the Norwegian Medicine Agency sets the pharmacies' maximum purchase price for all prescription medicines. These maximum prices are important to in relation to hospital purchases as well. ERP is applied when Hospital Procurement conducts its tender and negotiation process for hospital medicines. Hospital Procurement uses the maximum prices found through its ERP system, this is the maximum price which Norway is willing to pay for a certain medicine (Højgaard, 2016; Sykkehusinnkjøp, n.d.).

The process of determining the price can be boiled down to three steps.

[12]Previously known as Norway's Drug Procurement Cooperation (Legemiddelinnkjøpssamarbejd – LIS), but switched name to Sykkehusinnkjøp in July 2016 (Sykkehusinnkjøp, n.d.)

Step 1: The Norwegian Medicine Agency collects prices from the nine comparable countries – the reference countries. The countries are: Austria, Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Sweden and the UK. The three lowest prices are chosen from the reference list, and the average of those prices become the maximum price that the Norwegian government is willing to finance. Hence, Norwegian prices will always be among the three lowest prices at any product level (Apotekforeningen, 2008; Ognøy and Festøy, 2015). Companies are obliged, on request, to give Norwegian Medicine Agency information on the priced they charge in other markets. From the time of enquiry, the companies have 21 days to submit price details. The prices must be stated at the pharmacy purchasing price level (Ognøy and Festøy, 2015). The prices documented by companies are list prices and not transaction prices. Hospital Procurement typically starts a tender process after receiving the list prices to get the transaction prices in Norway (Kjellberg, pers. comm., April 4, 2018).

Step 2: The Norwegian Medicine Agency determines a markup which the medicine may be sold at.

Step 3: In the end a 25% tax is added, which is the maximum price pharmacies can charge its customers (Apotekforeningen, 2008).

The purpose of having maximum prices is to limit the growing medicine expenses (COWI, 2016). In addition, Norwegian Medicine Agency reevaluates the prices of the 250 – 300 most prescribed medicines annually, to ensure that the maximum prices reflect the price development in Europe. Changes in maximum prices can be due to pharmaceutical setting new prices, changes in exchange rates or pharmaceuticals being withdrawn from one of the reference countries (Ognøy and Festøy, 2015; COWI, 2016; Højgaard and Kjellberg, 2017).

10.4.3.2 ERP and stepped price model

The stepped price model was implemented in 2005, to manage the rising costs of generics. Medicines are initially priced based on the maximum prices derived through the ERP system, as the patent runs out and generic competition enters, the stepped price model is applied. It is the Norwegian Medicine Agency who decides whether the generic medicine is equal and substitutable to the branded medicines. If it is found equal and/or substitutable the stepped price model can start working. The stepped price model reduces the maximum price according to a predefined rate post patent expiration. The reduction depends on the annual sales for the previous year and the length of period since the competition was established (Nørregaard et al., 2012; Højgaard et al., 2017).

10.3.4 Norwegian external reference pricing – benefits and challenges

There are three main advantages of applying the Norwegian ERP model (see Table 10.2):

Table 10.2: Norwegian external reference price – benefits and challenges

Benefits	Challenges
• Can offer relatively low medicine prices • Offers mandate to negotiate with • Annual review of top 250 medicines	• Invalid as list prices are not transaction prices

Source: table by authors (2018) based on chapter findings

1) *Can offer relatively low medicine prices*. According to Frandsen (2015) the 25 most expensive medicines in Denmark was 17% more expensive than the exact same medicines in Norway. The article highlights that the main differences lies within the pricing models. Denmark has free medicine pricing under the voluntary price cap agreement sat, where the price cap is derived through ERP, this means that Danish prices must be below the average of all nine reference countries. This is not the case for Norway, which allows Norway favorable prices as it gives the country a mandate to negotiate (Frandsen, 2015). Hence, Norway can offer relatively lower priced medicines.

2) *Offers mandate to negotiate with.* As mentioned in the first point, the Norwegian ERP model gives payers a mandate to negotiate with, as the average of the three lowest prices is the maximum price.

3) *Annual review of top 250 medicines*. Another benefit of the Norwegian system is also the revision of medicines, in this way Norway can be sure that ERP allows up to date reference prices.

However, ERP has its shortcomings. The biggest shortcoming is getting the transaction price. In an e-mail correspondence with Weise, pricing researcher at the Norwegian Medicines Agency (Weise, pers. comm., May 2, 2018), he stated that it was not always possible to have access to the transaction prices. However, there is a European collaboration, EURIPID, fostering transparency which provides a database where prices were checked. Kjellberg (Kjellberg, pers. comm., April 4, 2018) pointed out that even though ERP in theory seems to be a good idea, the practical implications today is insignificant. List prices and transaction prices are not the same, which makes ERP difficult to use. However, Kjellberg (Ibid.) stated that ERP can be a point a of departure, but it cannot stand-alone. In absence of other solutions, ERP can be better than nothing (Ibid.).

Hence, even though Norway uses the ERP system and gets more favorable prices than many other countries, it is important to know the ERP is a system which is losing it validity, and the real prices of each countries are simply non-disclosed, making it impossible to purposefully apply ERP (Ibid).

10.4 Conclusion on external reference pricing system

ERP can be a good way to derive a benchmark or get an idea of what constitutes a fair price, at least in an international context. It is relatively easy to perform compared to VBP and profit control. Norway has been applying ERP and has achieved more favorable prices in some areas. However, ERP is not perfect. ERP can only work if transaction prices of medicines from reference countries are available, and this might not always be the case. Hence it can be challenging to use ERP, but ERP still provides some sort of base which the payers can start with in a negotiation situation. ERP can be considered when there is a desire to lower prices based on reference prices, a need for relatively simple model, and there is access to transaction prices and not only list prices. In addition, when implemented across many countries, ERP reduces the ability for pharmaceutical companies to price discriminate across markets. This potentially leads to lesser access to medicines in low-income countries, lower profits for pharmaceutical companies, and higher prices of medicines in high-income countries.

11 Recommendation – addressing identified challenges

11.1 Introduction

In the analysis of the Danish medicine pricing system in Chapter 7, this paper identified five challenges which prevent the achievement of fair pricing while still supporting innovation. In Chapter 8, 9 and 10, this paper assessed VBP, profit control and ERP pricing models and identified the advantages and challenges of each model (an overview can be found in Table 11.1). Case studies on England and Norway have been referenced to show how the pricing models worked in practice.

Table 11.1: Overview of pricing models

	Value-based pricing	External reference pricing	Profit control
Pros	• Lower incentives for me-too medicines • Creates incentives for pharmaceuticals to innovate • Directs pharmaceuticals innovation • Incentives of payers and pharmaceuticals are aligned • Perceived as "fair"	• Simple and easy to perform • Easily understood by the public • Reassurance to the public of comparable prices • Can drive down cost	• Easy to communicate • Gives the feeling of fairness • Avoid extreme price gouging
Cons	• Measuring value of medicine can be challenging • Data sources shall be chosen carefully • Changing evidence base can be hard to follow-up on • Not effective when generic medicine enters the market • Does not consider affordability	• Can be subject to model manipulation • Difficult to measure impact • Not all transaction prices are available • Unreliable sources can make the model invalid	• Bureaucratic and costly to administrate • Not taking the interest of pharmaceutical companies • Price does not necessarily reflect value • Creates the wrong incentives
Use	• Desire to maximize health outcomes given a limited budget • Desire to limit me-too drugs • Desire to encourage innovation • Resources to implement health technology appraisals • Competencies to understand both benefits and limitations of VBP • Applicable to branded medicines, not generic medicines	• Desire to contain costs • Need simple easily understood pricing model • Need easy to perform model • Desire to set prices similar to reference countries • Have access to reference countries medicine transaction prices, and not only list prices	• Desire to contain costs • Need simple easily understood pricing model • Need to limit profit of companies • Cost of administration does not exceed the benefits gained

Source: table by authors (2018) based on findings

This section aims to address the challenges which have been identified by applying the principles of the investigated pricing models. Additionally, the challenges are addressed by applying insights from

the twenty expert interviews conducted (an overview of the interviewed experts be found in Appendix B). Thus, this section addresses the fourth research question on how the challenges associated with pricing medicine can be addressed in the Danish public healthcare system. Table 11.2 shows the identified challenges.

Table 11.2: Overview of identified challenges

#	Theme	Challenge
I	Health Technology Appraisal	How to price medicines while rationally containing costs?
II	Generic monopolists	How to combat price gouging among generic monopolists?
III	Precautionary principle	How to incentivize broad public health innovation?
IV	Price cap agreement	How to overcome adverse effects of price cap agreement?
V	Price cap agreement	How to ensure price cap agreements remain effective?

Source: table by authors (2018) based on findings

11.2 Pricing medicine and rationally containing costs

"What should we pay for medicine?" This question has become highly relevant in most healthcare systems throughout the world, including Denmark. New medicines are constantly being developed and with patents protecting the pharmaceutical companies, high prices on medicines are driving up medical expenditures. From the payers' perspective, in this case the Danish public healthcare system, this naturally leads to the challenge of how to contain costs rationally, while still rewarding innovative pharmaceutical companies.

Challenge I: How to price medicines while rationally containing costs?

11.2.1 Applying measures of value-based pricing

VBP could give an answer to how much medicine should cost. In Denmark, the concept of VBP has been implemented to some extent with the introduction of the Danish Medicines Council ("DMC"). When pharmaceutical companies wish to introduce its medicine to the Danish hospital system, must go through the DMC's cost-effectiveness evaluation. Hence, the Danish government seems to support the fundamental principles of VBP. However, as this paper will demonstrate, the Danish Government should consider utilizing more measures from VBP.

The following section covers:

(1) The utilization of QALY (where the quality of life measure is obtained through RCT surveys) and whether the DMC should incorporate this measure as part of its cost-utility analysis. (2) The

utilization of RWD through an RWD system (a data system which accumulates healthcare related data) and whether Denmark should consider increasing its efforts in utilizing this data. (3) The utilization of risk-sharing agreement and whether Denmark should use risk-sharing agreement based on findings from interviews and pricing models.

11.2.1.1 Utilizing QALY from RCT for health technology appraisal

Currently, Denmark does not apply QALY in the hospital sector's health technology appraisals, which accounts for 60.2% of total medicine expenditure from the public government (Medicinrådet, 2017; Albinus, 2018). Instead, the current health technology appraisals procedure relies on the Danish Medicines Council ("DMC") categorizing the medicine into one of six categories of added clinical value. This is described in further detail in Chapter 6. With QALY being recognized as a cost-effective assessment tool adopted extensively in England, the question is whether Denmark should also start applying QALY when evaluating hospital medicines.

Table 11.3: Overview of QALY discussion

Discussion topic: Should the Danish medicine council implement QALY?	
Benefits	**Challenges**
• QALY is good cost-effectiveness measure • Proven and recognized cost assessment tool • Allows transparency in health technology appraisal	• Less flexibility • Fails to capture ethical, situational and other important aspects in health technology appraisals

Source: table by authors (2018) based on chapter findings

Most of the interviewed experts, professionals with experience in health economics, supported the idea of implementing QALY (Pedersen, pers. comm., March 21, 2018; Hedebye, pers. comm., March 23, 2018; Kjellberg, pers. comm., April 4, 2018; Gandjour, April 4, 2018; Goldman, pers. comm., April 12, 2018). They all agreed that QALY was an imperfect model, but believed it to be a good measure of cost-effectiveness relative to the current lack of cost-effectiveness measure. Used correctly, QALY gives an efficient distribution of value for both payers and sellers (Ibid.).

Another advantage mentioned in the interview was transparency (Ibid.). QALY would give the DMC an extra dimension of transparency in its health technology appraisals. This would be especially useful for the DMC, as the analysis in Part 7.1.2 argued that the lack of transparency in evaluation methods may hurt the sustainability of the DMC. The example that was presented was the case of Spinraza, where the DMC and Amgros were both criticized for not being transparent in terms why Spinraza was rejected. This caused negative media and political attention for the newly established council (Torpegaard, 2017).

Nevertheless, QALY is not without flaws. The director of the DMC, Klein, mentioned that implementing QALY could lead to less flexibility and more administrative work. In England, where NICE uses QALY to measure effectiveness, the time of appraisals can take as much as 290 days, whereas the DMC has 84 days to make its appraisals (Klein, pers. comm., March 3, 2018). The NICE process sometimes includes other activities in addition to the cost-effectiveness appraisal, which contributes to increased time usage. However, for some life-threatening disease like cancer, NICE can speed up the process. In any case, if implementing QALY would lead to longer times of introduction of new medicines, it would, ceteris paribus, lead to worsened patient access to medicines. In terms of overcoming inflexibility with having an official measure, Goldman (Goldman, pers. comm., April 12, 2018) proposed that QALY could be implemented as a supplementary measure, but the final decision should still be achieved through the council's discussion. This could satisfy the need for transparency, while allowing some flexibility for the decision-makers (Ibid.).

However, Goldman (Goldman, pers. comm., April 12, 2018) argued that QALY was lacking in multi-dimensional factors. From a theoretical perspective, it is argued that two different medicines with the same QALY score rarely create the same exact value for patients. As an example, one medicine cures an eye infection preventing blindness, while the other extends a patient's life for an additional six months. To compensate for this, NICE has included principles which include some degree of flexibility. For example, NICE allows multipliers to be used for end-of life treatments, thereby giving these treatments a larger threshold (Chalkidou, pers. comm., April 25, 2018). In order to attribute more accurate value scores to each medicine, QALY could consider various other factors such as patient independence post-treatment, patient life extension, or future medical needs, and assign multipliers accordingly. Goldman (Ibid.) also mentioned that if two different medicines were valued at the same cost-effectiveness, QALY does not consider that one could be more innovative. To improve the QALY measurement, it is recommended that additional measures of innovation to be considered in order to offer sufficient reward for innovation (Ibid).

Other disadvantages of QALY covered in Part 8.6.5 include methodological challenges, ethical considerations, as well as context or disease specific considerations. These are universal challenges which Denmark could face if QALY were to be applied, and must be considered. They are not impossible to overcome, but blindly applying QALY with modest knowledge level is not necessarily beneficial. One must know its strengths and limitations.

In conclusion, if the Danish public healthcare system were to follow the advice from the interviewed experts, they should consider implementing an effectiveness measure such as QALY. It has been applied in England, it is a good cost-effectiveness measure, a well-recognized tool, and offers transparency. The Danish payers must ensure that they understand QALY's strengths and limitations, and thus work with supplemental measures to compensate for the various factors that QALY is unable to address. QALY in itself might not cover all the complexity of health technology appraisals, and therefore it is important to add additional features e.g. multipliers on certain diseases or conditions.

Recommendation I: Utilize QALY in health technology appraisal

11.2.1.2 RWD and VBP in Denmark

The current stage of *real-world data* ("RWD") utilization in Denmark remains at a nascent stage. This was confirmed by all the experts who were working with RWD in Denmark, (Toft, pers. comm., March 9, 2018; Hammer-Helmich, pers. comm., March 13, 2018; Petersen, pers. comm., March 21, 2018; Samuelsen, pers. comm., March 22, 2018). Furthermore, Sonne (Sonne, pers. comm., Feb. 16, 2018) confirmed that RWD was not applied at Amgros today and Klein also confirmed the absence of RWD used in the decision-making by Danish Medicine Council (Klein, pers. comm., March 22, 2018). Hence, RWD is at a fairly nascent stage, which poses the question of whether Denmark should invest in utilizing real-world data to a further extent (the discussion overview is seen in Table 11.4).

Table 11.4: overview of RWD discussion

Discussion topic: Should real-world data be implemented to support VBP in Denmark?	
Benefits	**Challenges**
• Contribute to cost-effectiveness decisions • Denmark has a centralized CPR system • Can be beneficial for payers in terms of fair price • Can be beneficial for pharmaceutical industry in terms of a fair price	• High costs related to implementation • Institutions that invest will not receive direct benefits • Gains are rarely seen in the short-term • Need to overcome silo thinking across regions • Small population • Data privacy laws

Source: table by authors (2018) based on chapter findings

An advantage of RWD is that it can help determine the value of medicines in health technology appraisals. This can help Denmark to make cost-effectiveness decisions based on more realistic data because there are often discrepancies between clinical trial and real patient results (see Table 8.2 for a comparison) (Dilokthornsakul, Chaiyakunapruk and Campbell, 2015). For example, a medicine may be shown to have very rare side effects from its RCT. However, when the medicine is used in

the Danish public healthcare system, the RWD shows that the side effects are significantly more common. This is a case where the Danish government could use the obtained data to negotiate a lower price for the medicine, as it is not performing as well in real-life as in a RCT. Therefore, RWD and RWE can help the Danish government implement VBP to a higher degree to get a fairer price based on real world results.

Another argument supporting the implementation of RWD is the fact that Denmark has centralized healthcare data gathered on the Danish population through the Danish Civil Person Register ("CPR") (Hammer-Helmich, pers. comm., March 13, 2018). The CPR contains large amounts of data on the Danish population as it has collected healthcare data on all citizens since 1968 (CPR, 2018). Additionally, the data is very centralized, as opposed to countries such as the USA where data is scattered across insurance companies and private hospitals (The Commonwealth Fund, 2017). The centralized system with masses of historical data provides a great foundation in terms of implementing and utilizing RWD. Hence, the barriers of entry regarding RWD may be lower relative to other countries.

Moreover, the interviewees from the payers' side also noted potential benefits of implementing RWD. Sonne (Sonne, pers. comm., Feb. 16, 2018) expressed that he acknowledged the potential for RWD to offer valuable negotiation support. However, Sonne (Ibid) also expressed his concerns regarding the cost of implementation. Søndergaard (Søndergaard, pers. comm., March 7, 2018), Department Head for Ministry of Health (Sundheds- og Ældreministeriet), believed that RWD is a tool which will be used much more in the future, both in terms of understanding medicine effectiveness and detecting side-effects (Ibid.). In practice, Søndergaard believed that it would be possible to track medicines on the market to see its effects in a less controlled environment. In the real world, patients may consume alcohol or fail to accurately follow instructions regarding their medicine consumption. Evidently, the stakeholders on the side of payers are showing interest in RWD, and believe it could be beneficial for Denmark in the coming years.

The experts interviewed from the industry also believed that RWD could be beneficial for the pharmaceutical industry. Danish pharmaceutical companies such as Lundbeck and Novo Nordisk have just begun investigating the usage of RWD and RWE. In the interview with Hammer-Helmich, who is the Real-World Evidence Lead at Lundbeck (Hammer-Helmich, pers. comm., March 13, 2018), she stated that, in addition to being aligned with the incentives of payers, RWE could also offer pharmaceutical companies a fair justifiable price, which is also why Lundbeck has committed

resources into exploring the potential uses of RWE. Samuelsen (Samuelsen, pers. comm., March 22, 2018), from Novo Nordisk, also believed that RWD could be utilized by the pharmaceutical industry. Both companies are exploring the potential of using RWD, in collaboration with IBM Watson.

However, not all experts agreed that RWD would be expected to be used in medicine pricing in the future. Pedersen, professor at the University of Southern Denmark (Pedersen, pers. comm. March 21, 2018), noted that results generated from RWD are inherently flawed. He critiqued the internal validity of evidence based on RWD, noting that there are too many factors in which RWD does not consider. Furthermore, he stated (Ibid.) that RCT is also conducted in a real-world setting, as it is real world patients that are participating in trials, of course with the modification that the patients are carefully selected. Therefore, Pedersen did not recognize the benefits of implementing an RWD system (Ibid).

Another concern regarding RWD was the cost of implementation. Sonne expressed his concerns regarding the cost of introducing such a system, and questioned its worth (Sonne, pers. comm., Feb. 16, 2018). He believed that if the cost of implementation was higher than the benefits, there would be no reason to implement it. As an example, if all doctors were required to spend additional time documenting patient results in order to contribute to RWE, then it might be too resource-intensive and cost-ineffective (Ibid). Hammer-Helmich, Bjerrum, and Samuelsen all agreed that implementing the RWD system would require heavy investments (Hammer-Helmich, pers. comm., March 13, 2018; Bjerrum, pers. comm. March 22, 2018; Samuelsen, pers. comm., March 22, 2018).

Hammer-Helmich (Hammer-Helmich, pers. comm., March 13, 2018) also raised the concern in terms of the institutional incentives in Denmark. She mentioned that the parties who would be required to invest in new RWD systems may not be the most obvious benefactors of the system. As an example, the investment would likely not be funded by Amgros' nor the Danish Medicine Council's budget, but rather by a governmental institution like the Danish Health Authority's (Sundhedsstyrelsen). However, the benefits of such a system would likely accrue mostly to Amgros, the DMC, pharmaceutical companies and researchers. Therefore, there may be a lack of political incentives to push for the implementation of an RWD system. This was considered a hurdle, which could make implementing it politically difficult (Ibid). However, Hammer-Helmich suggested a *co-financing solution between the pharmaceutical industry and the Danish government*, as both parties would achieve benefits of such a system (Hammer-Helmich, pers. comm., March 13, 2018).

Samuelsen (Samuelsen, pers. comm., March 22, 2018) also noted that the benefits of implementing the system might not be fully realized in the short run. Currently, Denmark's utilization of RWD is

still at a nascent stage. This indicates that the investors, who invest in RWD today, might not necessarily be able to enjoy the benefits of the investment. Even though none of the experts could tell when it was possible to optimally use RWD in the Danish healthcare system, they agreed that the implementation of such a system is not in the immediate horizon (Hammer-Helmich, pers. comm., March 13, 2018; Bjerrum, pers. comm. March 22, 2018; Samuelsen, pers. comm., March 22, 2018). Samuelsen provided an example where the regulatory setting was not ready for RWD. This is exemplified in the fact that the FDA has just announced that it would publish guidelines around assessment of safety and effectiveness regarding RWD in 2021. Hence, being able to actually utilize the data and RWE found would take a considerable amount of time (Ibid.).

In practice, the competitive culture seen across the Danish hospitals also poses a challenge (Toft, pers. comm., March 9, 2018). Toft, who works at IBM and has previously implemented systems in Danish hospitals, expressed concerns that there exists a hostile data sharing culture across hospitals in different Regions. He identified silo thinking and reluctance to help each other. Toft identified this cultural aspect as one of the bigger challenges in terms of successfully utilizing RWD in Denmark (Ibid).

Data privacy regulation could also be a barrier to the implementation of RWD. However, Søndergaard (Søndergaard, pers. comm. March 7, 2018) believed that if there were strong support and evidence for RWD being beneficial for health technology appraisals, then it is likely that a solution to accommodate RWD could be introduced in legislation. Another concern regarding data privacy was hacking. In the interview with Bjerrum (Bjerrum, pers. comm. March 22, 2018), he believed that if an RWD system should be implemented, it would be important to take account the risk of a breach of confidentiality of personal data. He expressed that it would be less risky to have different databases rather than a centralized database, making it more difficult for security breaches of the Danish healthcare data (Ibid.).

In 2017, Denmark had a population of 5.7 million (DST, 2018). Hammer-Helmich (Hammer-Helmich, pers. comm., March 13, 2018) expressed that due to the small population in Denmark, it could be challenging for Denmark to create any valuable RWE on certain diseases. As an example, if there were only 500 patient cases pertaining to a disease, it would be challenging to get better insights compared to RCT, which often has more participants (Ibid). Therefore, Hammer-Helmich suggested that it could be more interesting to have a collaboration across Scandinavia (Ibid).

In conclusion, both the industry as well as the government institutions were supportive around the idea of introducing an RWD system. However, experts also agreed that there were challenges ahead with increasing the utilization of RWD. The issues identified were the risk of a potentially costly system, a long-term investment project with little short-term gain, a lack of return for early investors of the system, silo-thinking across hospitals, a small Danish population, and data privacy concerns. Whether or not to implement RWD requires more research and calculations. However, based on research and expert opinions, it seems that having an RWD system could give benefits in the long-run. Hence, from a long-term perspective, implementing RWD has its benefits, but the short-term implications are inconclusive.

As there are many great benefits related to RWD, the paper recommends the Danish government to co-invest with the industry to further utilize RWD. From the interviews with both Hammer-Helmich and Samuelsen, the industry seems willing to explore RWD further, and it is important that the Danish government influences the direction of how RWD is being used in order to align the interest of the government and the industry. Therefore, the Danish government could experiment with such a system and implement trials where diseases with direct measurable outcomes could be tested to see if RWD could really work and provide true value to pricing medicine.

Recommendation: Utilize RWD through co-investment with the industry, potentially in pan-Scandinavian collaboration

11.2.1.3 Risk-sharing agreements

Risk-sharing agreements ("RSA") are also a way to implement VBP in Denmark. Amgros experimented with RSA on medicine for the treatment for melanoma in 2015. However, it was concluded that RSA had a solid theoretical foundation, but was difficult to implement in practice due to the administrative costs outweighing savings and benefits (Lynge, 2015). This was further supported by the interview with Kjellberg (Kjellberg, pers. comm., April 4, 2018), who expressed that in theory, RSA has many benefits. However, in practice, administrative work would pose a challenge as a working group would have to follow-up and determine each RSA case, defining the parameters through which a patient could be determined as cured or otherwise successfully treated. Kjellberg also mentioned that in practice, RSA could also lead to large legal fees in cases of disputes, especially when the results were ambiguous. As an example, if a pharmaceutical company was unsatisfied with the results of Amgros' assessment of a medicine (e.g. ambiguous results, medicine not effective), they could sue Amgros and the legal expenses could easily outweigh any savings. In

addition, Grossman and Hart (1986) and Hart (1995) argue that, in the field of economic contract theory, contracts would not be able to specify all cases in every possible contingency, and the cost of writing a complex contract can be very high. Hence, RSA is theoretically a good idea, but in practice it might be more costly than beneficial.

Recently, the Danish government published a new growth plan for life science on March 2nd, 2018. One of the initiatives in the growth plan was to implement a pilot scheme for the introduction of risk-sharing into the medicine subsidy system in the primary sector. The pilot will run until the end of 2021, where RSA will be reevaluated (Erhvervsministeriet, 2018; Hildebrandt, 2018). In a press release, the Danish Minister of Health, Ellen Trane Nørby, stated that Danish patients shall be among the first to benefit from life improving treatments which should be secured through risk-sharing agreements (Erhvervsministeriet, 2018). It can be seen that there is an interest in RSA from the Danish government's side as patient access can be improved. This has been very well received by the pharmaceutical companies. Indeed, The Danish Association of the Pharmaceutical Industry, representing the researching pharmaceutical industry, has been advocating for RSA to be implemented. It will allow its members' products which were previously not reimbursable a new chance to be reimbursed. Novo Nordisk has also expressed its fondness of the new pilot project and is looking forward to the implementation (Hildebrandt, 2018). In the article by Hildebrandt (2018), Kjellberg expressed that even though it can be difficult for AMGROS to find the right way of utilizing RSA, it does not mean that RSA should be rejected entirely. Kjellberg thought the pilot was exciting, but expressed concerns over its complexity. However, he suggested that the Danish government could run the pilot on another health-related measure, such as obesity, where the relevant company would be responsible for the patient losing a set amount of their body weight (Ibid.). Moreover, when Amgros rejected the RSA in 2015, they only measured it through one case of melanoma. The initial implementation labor and investment costs were not divided over several cases, thus making the cost per case substantially higher. One could argue that RSA should be re-evaluated because the marginal cost of exercising RSA could be lower than the initial implementation for a single case.

Table 11.5: Overview of RSA discussion

Discussion topic: Should risk-sharing agreements be implemented in Denmark?	
Benefits	**Challenges**
• Government is supporting pilot project • Patient access to medicine • Companies get previously non-reimbursable medicines reimbursed	• High administrative costs • Contracts are imperfect • High complexity

Source: table by authors (2018) based on chapter findings

In theory, RSA can have many benefits, especially in terms of patient access to innovative medicines. It is an idea with potential and is supported by the Danish government through its pilot project. Despite the administrative and legal complexities, it is recommended that the Danish government continue to test RSA. However, it is recommended that the government carefully choose the medicines in the pilot project as the results need to be quantifiable and easy to measure. This paper also recommends that the Danish government try to expand its scope and run RSA pilot projects within the hospital system for a limited period of time. After the period, the agreement should be evaluated to see if such projects are worth implementing in the long run.

Recommendation: Run pilot projects on RSA on hospital medicines

11.2.2 Applying principles of ERP

The payers of hospital medicines in Denmark have already applied ERP through the existing price cap agreement in an attempt to obtain prices that are in line with other comparable countries. ERP may prove useful if reference prices are lower than the current price paid by Denmark. In this scenario, ERP could help to lower medicine expenditures. However, according to Kjellberg (Kjellberg, pers. comm., April 4, 2018) ERP does not work as effectively anymore. This is due to the fact that list prices, which form the basis for reference prices, are not transaction prices (prices after discounts). Therefore, using ERP to rationally contain cost might not be the best solution. Furthermore, ERP does not encourage innovation, as it is a tool built for price comparison among peers to ensure that the user is not over paying. It can be deduced that ERP is not built to fulfill the identified challenge I.

In practice, ERP does not support innovation, and its ability to contain costs in the long run is highly questionable. However, ERP could be supportive in terms of giving an idea on what prices might look like in reference countries. Therefore, this paper argues that ERP should not be implemented to any higher degree than it currently is today.

11.2.3 Applying principles of profit control

In theory, profit control could contain costs as the payer can put a limit on the amount of profit that a pharmaceutical company is allowed to make. One could also argue that, if the profit limit is set to a high enough point, it may also encourage innovation (e.g., imagine a profit limit at 40%). In the interview with Kjellberg (Kjellberg, pers. comm., April 4, 2018), he stated that profit control is an applaudable idea in theory, but its practical applications were highly ineffective. First, profit control is costly to administrate, and it has not yet been proven successful in England (see Part 9.4.2). Financial reports of the companies would also have to be investigated, along with the incentives for companies to manipulate financial statements. It was clear during the interview with Goldman and Kjellberg (Kjellberg, pers. comm., April 4, 2018; Goldman, pers. comm., April 12, 2018) that neither of them believed that profit control was merited as a tool to contain costs and support innovation. The cost of implementation was simply too high relative to the benefits.

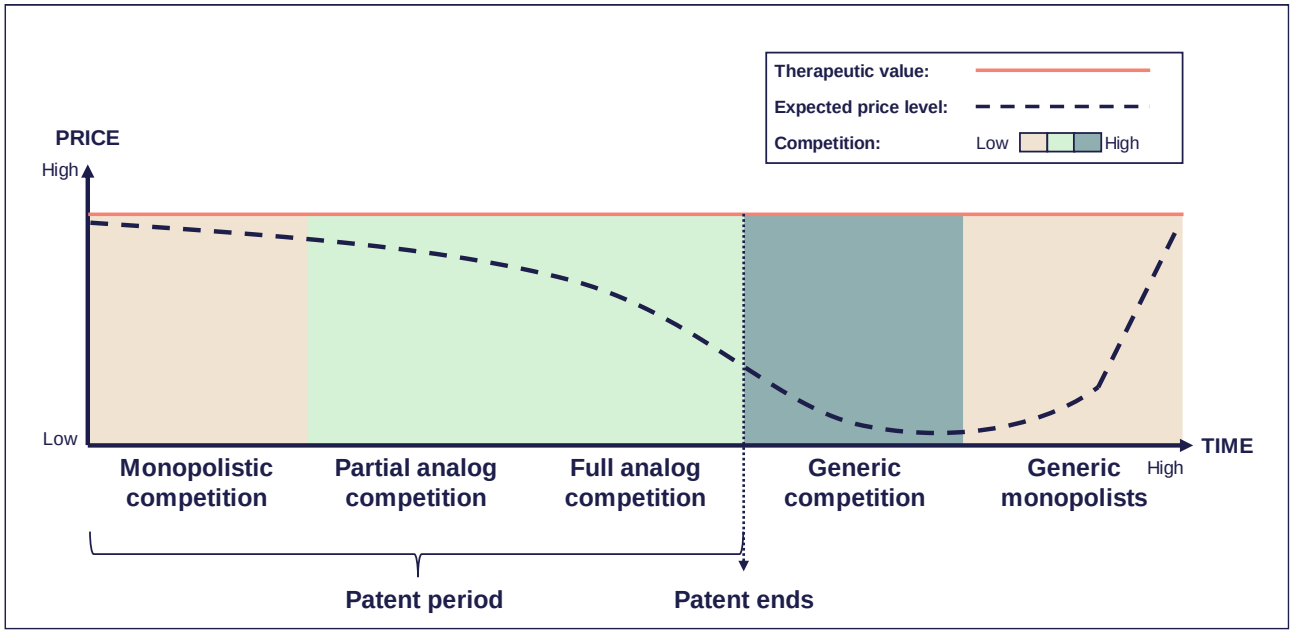
In conclusion, profit control has redeeming qualities in theory, but can be challenging to administrate and create the wrong incentives in practice. Therefore, the paper does not recommend the usage of profit control in the Danish healthcare system.

11.3 Generic monopolists

The life cycle of a patented medicine eventually leads to patent expiry and resulting generic competition. However, within generic competitors, cases are observed where one generic company outcompetes and/or acquires the other competitors. As covered in Part 7.1.1, this potentially leads to generic monopolists suddenly raising prices dramatically. This happened in Denmark in January 2018 in the case of Syntocinon, where Amgros was forced to pay an additional 6 million DKK. This can be in an issue in the short run as Amgros may not be able to secure alternative suppliers quickly. Hence, this is a challenge which was identified in the Danish context.

Challenge II: How to combat price gouging among generic monopolists?

Figure 11.1: Overview of competitive dynamics



Source: figure by authors (2018) based on interview (Sonne, pers. comm., Feb. 16, 2018)

11.3.1 VBP to combat generic monopolists in Denmark

VBP may not be a tool for combatting generic monopolists. One of the purposes of using VBP is to secure payers a "fair price" while balancing incentives for innovation. However, generic medicine manufacturers do not invest in R&D, and therefore do not contribute to innovation, as seen in Figure 11.1. Under monopolistic competition, where the innovator pharmaceutical company is under patent protection, it is expected to be able to its products in accordance with the product's therapeutic value (e.g. medicine price equals the therapeutic value), under VBP. As the patent expires, generic competition enters, and prices are forced down. If prices continue to drop, one generic supplier may end up supplying the entire market for the medicine, becoming a *de facto* monopolist. This generic monopolist may potentially raise prices as it wishes, as there is no regulation in Denmark preventing them to do so. This indicates that it would not be appropriate to price generic manufacturers under VBP.

11.3.2 ERP to combat generic monopolists in Denmark

In the hospital system, Amgros would have difficulties applying ERP as a measure to mitigating price gouging, as the generic monopolist would have a high bargaining power (from being the single supplier of a critical medicine) and Amgros would have no legislative mandate to enforce the prices with. Enforcing ERP as maximum prices through regulation could be a solution, e.g. by fining certain excessive price increase. This type of legislation has implemented in the US state of Maryland (Trager,

2017). This would offer the payer's side a mandate to negotiate with, which could make it more difficult for generic monopolists to implement its extremely high prices. Nevertheless, the challenge that Denmark may face using ERP is that the list prices from reference countries are not necessarily the transaction prices.

In an interview with Clausen from The Danish Association of the Pharmaceutical Industry and Søndergaard from the Ministry of Health (Clausen, pers. comm., Feb. 2, 2018; Søndergaard, March 3, 2018), both parties noted that the current voluntary price cap agreement was well-functioning and that it saved both parties complex and costly administrative work. In summary, the findings indicate that ERP (without additional legislation) cannot combat generic monopolists, as it is costly and not well-functioning due to unrevealed transaction costs.

11.3.3 Profit control to combat generic monopolist in Denmark

In an interview with Clausen from The Danish Association of the Pharmaceutical Industry and Søndergaard from the Ministry of Health (Clausen, pers. comm., Feb. 2, 2018; Søndergaard, March 3, 2018), both parties noted that the current voluntary price cap agreement was well-functioning and that it saved both parties complex and costly administrative work. In summary, the findings indicate that ERP (without additional legislation) cannot combat generic monopolists, as it is costly and not well-functioning due to unrevealed transaction costs.

In reality, profit control can be complicated to implement as the Danish government would have to investigate the financial reports of these generic monopolists. Thus, the administrative costs related to profit control can be high, which is supported by both Kjellberg and Goldman, who agreed that profit control was bureaucratic and very costly to implement (Kjellberg, pers. comm., April 4, 2018; Goldman, pers. comm., April 12, 2018). In addition, generic monopolists did not seem to be a widespread enough problem to warrant these costly controls, according to Sonne and Kjellberg (Sonne, pers. comm., Feb. 2, 2018; Kjellberg, pers. comm., April 4, 2018), as there were only a few cases related to monopolists abusing their market power. Additionally, the implementation of PPRS in England has not been regarded as successful as the British government had hoped for (Tillett and Arnold, 2017). Therefore, it can be questioned whether it is worthwhile for Denmark to implement profit control. However, if generic monopolies continue to become an increasing problem (as they have in the US and Canada), and the cost of implementing and administering profit control mechanisms is significantly lower than the cost caused by generic monopolists, profit control could be considered in the future.

In conclusion, profit control may not be an optimal solution to mitigate the risks of generic monopolists. It may act as a supportive mechanism, as implementing it as the primary solution would lead to considerable challenges. This leads to the consideration of alternative solutions, which are not covered by the investigated pricing models. These solutions are described in Part 11.3.4.

11.3.4 Alternative solutions not covered by pricing models

Buying in-bulk and keeping own stock could be a solution for the Danish government, in terms of combatting shortage of supply and excessive price increases. This was suggested in the interview with Kjellberg (Kjellberg, pers. comm., April 4, 2018). The advantage of buying in-bulk would be to overcome a sudden price pressure from generic monopolists, and shortage of supply. The Danish government could potentially store up the most essential medicines one year at a time. Vital medicines which might be threatened by generic monopolists should be targeted. In case of a generic monopolist taking control of a certain medicine price, the Danish government could even start producing its own generic medicines. Since small molecule drugs are easy to create, the techniques used are not considered to be highly complex (Danzon and Towse, 2003). This is in fact already seen in the US. A group representing more than 450 hospitals in the US are forming their own generic medicine company. The group is producing generic versions of around 20 existing medicines that the hospitals believe are currently too expensive or short in supply, and expects the first of its products to be available in 2019 (Mangan, 2018). Currently, Denmark has the hospital pharmacies (Sygehusapotekerne) where medicines for individual patients can be produced with the exact doses required by physicians However, Denmark does not produce its own generic medicines to combat generic monopolists (Sonne, pers. comm., May 4, 2018). Thus, Denmark could consider doing the same as the hospitals in the US, to starting its own production of generic medicines and even creating a pan-Scandinavian collaboration to co-invest.

This is, in fact, already seen in the US. A group representing more than 450 hospitals in the US is forming its own generic medicine company. The group is producing generic versions of around twenty existing medicines that the hospitals believe are currently too expensive or short in supply, and expects the first of its products to be available in 2019 (Mangan, 2018). Thus, Amgros could consider increasing the number of generic medicines they produce, starting with the medicines that are the most vital, and which exist in the least competitive markets. If economies of scale are desirable, it may be valuable to use pan-Scandinavian collaboration to co-invest in this production and share the fixed costs of starting production.

However, these suggestions are not without disadvantages. It could be difficult to predict the future demand and competitive situations of different medicines. Furthermore, there is a risk of medicine expiring while it is stocked. Producing own medicine has several complications, specifically the time to start up the production and the regulatory oversight. It is estimated that, due to regulatory documentation, starting the production of a new generic medicine takes as much as a year, depending on the specific medicine. For some medicines, the time needed to start production may be significantly lower.

However, in the long run, the Danish government already produces its own medicine through hospital pharmacies (Sygehusapotekerne).

At the time of writing, generic monopolists have not constituted a large problem for the Danish public healthcare system, except for singular cases. Therefore, it might not be worthwhile investing in costly and bureaucratic profit control mechanisms yet. However, generic monopolists remain a considerable risk. Thus, this paper argues that the combination of keeping a stock of critical, noncompetitive medicines would mitigate short term supplier risk, while long term supplier risk may be mitigated by starting own production of generic medicines, potentially in pan-Scandinavian collaboration.

Recommendation: Build-up own stock of generic medicines in the short run, and consider own production of generic medicines, potentially using pan-Scandinavian collaboration in the long run

11.4 The precautionary principle

The precautionary principle mandates the Danish Medicines Council to take extra precaution when assessing medicines that are likely to have high budget impact. Part 7.1.3 demonstrated the adverse effects of this principle, and used the example of innovative treatments for hepatitis C to show the potential costs of avoiding high-cost medicines.

The two main challenges that were identified are (1) patients are not given access to the most optimal treatment, and (2) pharmaceutical companies are not encouraged to invest in new treatments aimed large patient groups. Instead, pharmaceutical companies are developing more orphan drugs and more marginal medicines, instead of cures for bigger diseases (Goldman, pers. comm., April 12, 2018).

Challenge III: How to incentivize broad public health innovation?

It is important to understand that the precautionary principle comes from political regulation. Hence, it can be challenging for the pricing models to overrule political decisions. VBP may help justify the

high price of innovative medicines if their clinical or therapeutic value is proportionally high as well. ERP cannot be applied in this setting, as the model is used to lower the prices of medicines, rather than incentivizing new innovation. Similarly, profit control might not be that useful either, as limiting profits in itself does not incentivize further innovation. For these reasons, this section will not address ERP and profit control.

11.4.1 Applying VBP

Even if the precautionary principle remains in place, VBP can be used to encourage innovation for pharmaceuticals. It can be used to justify a high price for a medicine if the medicine is highly effective and safe. VBP does not inherently consider the size of the patient population. Additionally, VBP is not limited to any budgetary constraints. Hence, from if one focuses solely on VBP, the challenge seen in the case of hepatitis C should be solved. However, the extent to which prices can be determined through VBP are constrained by the public sector's allocated budget for medicines. Therefore, accepting medicines with large impacts on the budget reduce available funds for other types of healthcare.

11.4.2 Alternative solution – mortgage price agreement

In an interview with the authors of this paper, Goldman (Goldman, pers. comm., April 12, 2018) proposed a possible solution to managing medicines with large, up-front costs. Similar to how houses are generally financed, he suggests a *mortgage pricing agreement* to spread out costs over time. Like houses, expensive but cost-effective medicines are worthwhile investments, but they cannot feasibly be paid instantaneously. While the model was developed for the private pharmaceutical industry (Goldman, 2014), he notes that the model can also be applied to the single-payer public healthcare systems like Denmark. (Goldman, pers. comm., April 12, 2018).

The costs of not treating a disease with the most innovative medicine may be higher, in the long run, than the price of paying for the expensive medicine. The example of hepatitis C, described in Sub-part 7.1.3.1, is one situation where this may be the case. A similar rationale is how students are willing to take a loan to finance their private education. Amgros could consider entering into a contract with the pharmaceutical companies where they accept the high price of a medicine, but is able to defer payment to an agreed upon period of time in the future (e.g. 5 years). In this way, pharmaceutical companies would still be encouraged to innovate medicines with high efficacy for large patient groups, patients would experience increasing life quality, and the government would be able to manage their costs more controllably (Ibid.). VBP does not take into account the budgetary limits as well as the

time perspective, which is where the mortgage pricing agreement can play a supplementary role. Emergency funding could also be a solution. The Danish government could set up an Access to Breakthrough Fund, which funds medicines which are highly effective, but with large budget impacts. To gain access to this fund, the medicine must be considered breakthrough by some official guidelines (Goldman et al., 2014).

These suggestions are not without disadvantages. Having a mortgage pricing agreement can be unpredictable, as it can be difficult to predict how the future budget would develop. As for the emergency fund, it can be difficult to prioritize which disease group the fund should be granted to.

As such, if VBP principles are to be applied to a further extent than today, it is worth considering alternative financing models such as mortgage financing. However, it should be noted that it is important not to allow all expensive medicines to be financed through mortgage financing. Rather, the cases should be chosen carefully where the cost of not curing the disease immediately can be much more expensive in the future.

Recommendation: Test run pilot on mortgage financing for expensive curative medicines in cases that would have the highest patient impact

11.5 Price cap agreement's adverse effects

Due to the voluntary price cap agreement, the prices of new medicines are not allowed to grow at any point. This is the case even if the pharmaceutical company that markets the medicine discovers new evidence revealing that the medicine is more effective or safe than previously. This type of evidence could be discovered through methods like using RWE and/or conducting post-market studies. This is a challenge because it can lead to (1) discouragement of pharmaceutical to invest in post market studies/RWE, and (2) incentives for pharmaceutical to price its medicine as high as possible at introduction, since prices cannot increase after (Samuelsen, pers. comm., March 22, 2018).

Challenge IV: How to overcome the adverse effects of the price cap agreement?

11.5.1 Mitigating inflexible prices

A static and rigid price cap is not in accordance with VBP principles. VBP principles simply advocate for the principle that price should be aligned with value that the product or service confers. Therefore, if evidence that supports an increase of a medicine's value arises, then the price of the medicine should rise accordingly under VBP.

In the interview with Goldman (Goldman, pers. comm., April 12, 2018), he mentioned that he was working on a paper describing a new model for pricing medicines. The model suggests that medicines should initially be priced at a low point to give patient access and to provide an opportunity for pharmaceutical companies to prove its real-life effectiveness, rather than relying on efficacy in RCT. As the medicine proves its efficacy in real life, the company should be able to raise prices in accordance to its value, thus minimizing the risk of paying in excess for ineffective medicines. During this period, the pharmaceutical company would be able to achieve reasonable returns on its investment, recouping the costs of developing the medicine. As the patent runs out, the medicine can be subject to generic competition, hence lowering the price. This model utilizes VBP principles to their full extent, and considers the usage of real world evidence. The disadvantages associated with this model are that it might be perceived as unfair or unethical from the patient's perspective if the price suddenly increases, even if it may be justified by VBP. The price increase might also be difficult to understand for the greater public, possibly resulting in public disapproval or political involvement, similar to what has been observed in the case of nusinersen (Spinraza). Therefore, it might be politically challenging to implement such a model.

Profit control does not inherently help solve the challenge, as it only limits prices and does not consider incentives to perform post market studies. However, in England, profit control is exercised through the PPRS model, and contrary to the price cap agreement in Denmark, PPRS allows pharmaceutical companies to increase its prices every year. Furthermore, if new evidence is found, pharmaceutical companies will be allowed to set a new price for its medicine. Evidently, more flexible prices are seen in England. Thus, it is apparent that while profit control does not necessarily solve the problem in itself, implementing profit control is not in contrast with mitigating the issue of inflexible price caps.

While the ERP mechanism of the price cap agreement is the reason that this challenge exists, ERP could be implemented in a way where this challenge would not be present. Under a pure ERP model, with no rigid price cap, the price would follow the reference prices in the reference countries and fluctuate accordingly, such as if prices increased in other countries due to new evidence being discovered. Thus, it is noted that ERP is a comparison tool which, by itself, neither encourages nor discourages pharmaceutical companies to conduct post-market studies. An exception to this is if the degree of cross-reference between countries is so high that it is not possible to increase prices in any country, because every country relies on other reference prices to set price caps.

In conclusion, a static unchangeable price cap is not beneficial. If implemented alone, profit control and ERP are not useful in situations to combat pricing issues. However, principles of VBP could be applied to allow companies to change their prices if new evidence supports it.

Recommendation: Allow price adjustments if new evidence justifies it

In this section, it is argued that some of the mechanisms of the price cap agreements may hurt access to medicines, reduce the ability for pharmaceutical companies to apply RWE in pricing their medicines, and create ineffective practices to limit excessive prices for medicines.

11.6 Price cap agreement becoming ineffective

In Denmark, domestic drug prices are only benchmarked against international reference prices to a limited extent (i.e. every 3rd, 6th and 9th country in which the drug is introduced). It also encourages pharma companies to strategically time their market entry of a new medicine across countries. Because price caps are reviewed so infrequently, they often become outdated and no longer reflect the up-to-date international market price.

Challenge V: How to avoid price cap agreements from becoming ineffective?

11.6.1 Review reference prices

As ERP is not reviewed regularly, it will not reflect the real prices in the reference countries. A way to overcome this is to learn from the Norwegian ERP model. In Norway, the prices of the 300 most prescribed medicines are reviewed annually. This could be implemented in Denmark as well to see if there are any other countries which are receiving an even better price for the medication. However, if the ERP model should be applied, it is important to take into account the flaws it has (e.g. list prices are not the same as actual prices). This recommendation can be implemented fairly easily and it assumes that the Danish government desires to continue with ERP system in the price cap agreement.

Recommendation: Review reference prices continually

11.7 Sub-conclusion

This chapter covered the challenges which were identified in the Danish healthcare system and addressed them through the investigated pricing models, interview findings, and alternative solutions. In Table 11.6 the challenges and, and the recommendations that this paper presents are summarized.

Table 11.6: overview of challenges and recommendations

#	Challenge	Recommendation
I	How to price medicine, while rationally containing costs?	• Utilize QALY in health technology appraisal • Utilize RWD through co-investment with the industry, potentially in pan-Scandinavian collaboration • Run pilot projects on RSA in hospital sector
II	How to combat price gouging among generic monopolists?	• Build-up own stock of generic medicines in the short run, and consider own production of generic medicines, potentially using pan-Scandinavian collaboration in the long run
III	How to incentivize broad public health innovation?	• Test run pilot on mortgage financing for expensive curative medicines in cases that would have the highest patient impact.
IV	How to overcome adverse effects of price cap agreement?	• Allow price adjustments if new evidence supporting it is found
V	How to avoid price cap agreements from becoming ineffective?	• Review reference prices continually

Source: table by authors (2018) based on findings

To address challenge I: *"How to price medicines while rationally containing costs?",* it was found that the Danish public healthcare system could apply principles of VBP through: (1) Utilizing QALY in health technology appraisals, (2) utilizing RWD through co-investment with the industry, and (3) running pilot tests on RSA in both the primary and hospital system. ERP was not recommended, as it was both costly due to unrevealed transaction prices (prices after rebates). Profit control was also found to be too heavy in administrative costs and complex to manage given the benefits.

In terms of challenge II: "*How to combat price gouging among generic monopolists*?", it was found that VBP, ERP, and profit control pricing models were not the best way to address the generic monopolist in Denmark. However, an alternative solution to build-up own stock of generic medicines in the short-run, and consider own production of generic medicines, potentially through pan-Scandinavian collaboration in the long run were found to be the most effective as it would lower the bargaining power of the generic monopolist.

Challenge III created by the precautionary principle: "*How to incentivize broad public health innovation?*", it was found that VBP principles could be applied if the Danish government used an alternative financing method such as mortgage finance to pay for innovative medicines. Therefore, it should test run pilot on mortgage financing on expensive curative medicines with high patient impact.

Challenge IV: "*How to overcome the adverse effects of the price cap agreement?",* it was found that ERP and profit control would be ineffective. Profit control does not encourage post market studies and neither does ERP. Hence, VBP principles should be applied as it would allow new evidence into the picture. Thus, it is recommended that price adjustments should be allowed if new supporting evidence was found.

Challenge V: "*How to avoid price cap agreements from becoming ineffective?*", the solution to this challenge was found to be to review the references prices continually in a similar manner to Norway.

12 Conclusion

This paper set out to address the following problem statement: *From the perspective of payers, what is the most sustainable model for pricing hospital medicines in the Danish healthcare system?* In determining the most sustainable model of pricing hospital medicines in the Danish public healthcare system, this paper identified and explored three main medicine pricing models: value-based pricing, profit control, and external reference pricing. While it was found that the models were effective at solving many of the identified challenges, no model is perfect in isolation. In instances where the medicine pricing models were not able to solve the identified challenge, alternative recommendations were identified.

Value-based pricing was found to be an effective model for pricing medicines. Specifically, applying its principles is found to enable efficient allocation of resources, by using the standardized effectiveness measure quality-adjusted life years. This also increases transparency of medicine evaluations. New methods of measuring value, such as using real-world evidence, have the potential to improve value-based pricing models further. In addition, risk-sharing agreements may become effective contractual agreements for lowering the risk of overpaying for ineffective or unsafe medicines. The main issue with value-based pricing was the difficulty in measuring value objectively.

Profit control provides many theoretical benefits, but an analysis of its application in the United Kingdom displays the model's practical limitations. Profit control was determined to be potentially useful in avoiding excessive prices, but the administrative costs of implementing such a system can be significant.

External reference pricing is a simple and potentially effective model for lowering prices. However, it was found to be fundamentally flawed, as hidden transaction prices may reduce the model's usefulness, with companies dodging its mechanism of action. Furthermore, external reference pricing leads to convergence of prices internationally, potentially hurting patient access, lowering company profits and increasing prices.

In conclusion, value-based pricing was found to be the medicine pricing model that was most effective at securing fair prices, balancing the interests of payers, patients and the pharmaceutical industry. Profit control and external reference pricing may have their niche uses in lowering costs of medicines, but they may also hurt patient access and they fail to incentivize new innovation in medicines.

13 Discussion

13.1 Implications of findings

This paper presents a list of recommendations that may be implemented by policymakers in the Danish public healthcare system. It is argued that the paper presents a worthwhile contribution to the existing literature by providing an in-depth analysis of the applicability of different pricing models on the Danish public healthcare system. Furthermore, the aim of not just lowering cost, but rather trying to form a sustainable model of pricing by also considering effects on patient access to medicines and effects on innovation.

It is argued that the applicability and relevance of this paper is high. During the writing of this thesis (on March 2nd, 2018), the Danish Ministry of Industry, Business and Financial Affairs published a report titled *Growth Plan for Life Science*. The report solidifies the importance of the pharmaceutical sector to the Danish economy. Furthermore, some of their recommendations are in line with the ones presented in this paper, an example being that of recommending introducing pilot programs with risk-sharing agreements. In addition, the continued discussion and controversy surrounding the decision on nusinersen shows the relevance of the proposed recommendations regarding transparency in the appraisal system. Similarly, the upcoming treatment guidance on hepatitis C may prove to be the first application of the Precautionary Principle, which is considered sub-optimal by this paper. It is noted that the model of the Danish Medicines Council is up for evaluation by January 2019 (Danish Regions, 2016). This paper thus presents a possible point of departure for this discussion of the potential shortcomings of the model and possible improvements to further the cause of the Danish Medicines Council. Furthermore, it is argued that the recommendations presented in this paper can feasibly be implemented without the need for significant changes in legislation. At most, it is expected that the mandate of the Danish Medicines Councilacit and Amgros would have to be expanded to accommodate recommendations like pilot-testing risk-sharing agreements and utilizing quality-adjusted life years in medicine evaluations.

13.2 Limitations

There are several important limitations to this paper. First and foremost, the paper only looks in detail at the Danish public healthcare system. As the total expenditure on medicines by the Danish healthcare system accounts for a very small proportion of global expenditures (OECD, 2008), it is unlikely that pricing decisions in Denmark have any significant effect on innovation globally (Hedebye, pers. comm., March 23rd, 2018). However, this paper argues that it is a moral duty for a

wealthy country like Denmark to contribute its fair share of the global costs of innovation. Furthermore, the identified challenges are tied to the existing health technology appraisal system in Denmark, as well as the specific legal and political framework. Thus, while the recommendations of this paper may be transferable to other healthcare systems in other countries, this relies on assumptions of similarity between healthcare systems in the countries in question and that of Denmark. Furthermore, this paper only considers three types of pricing models, i.e. value-based pricing, external reference pricing, and profit control. The use of other models, such as basing price on real world evidence and the use of risk-sharing agreements, are covered under these models, but could easily warrant an entire research paper in their own right. Furthermore, this paper does not provide recommendations on changing legislation on topics such as patents and parallel trade, despite these having been empirically shown to be impactful on both the affordability and access to medicines, as well as having effects on innovation.

The perspective of producers of medicine and patient could also have been included to a higher degree. Because of the significant complexities of the models and the regulatory landscape of medicines, the scope of this paper did not permit an in-depth analysis of how pharmaceutical companies could respond to the policy suggestions that this paper recommends. Furthermore, a greater understanding of patient organizations' efforts to promote fast access to medicines could have been insightful, but was limited due to both scope and access to appropriate interviewees. Finally, several of the recommendations that are presented require further cost-benefit analyses to determine the appropriate course of action. Profit control is one such example, as the model may prove useful in some cases, but the fixed costs of administration may exceed the benefits in other cases.

13.3 Further research

This paper fosters the potential for a great deal of further research. One key piece of further research could be to analyze appropriate strategic responses to the policies that are recommended in this paper, taking the perspective of the producers. Additional research could also be conducted with the aim of generalizing the findings of this paper, making them transferable to a higher degree to other countries. This paper also recommends conducting pilot programs involving the use of real world evidence and risk-sharing agreements. If implemented, these programs could be the focus of case studies to determine the effectiveness these approaches. Finally, quantitative studies of the effect of the recommendations could be performed, potentially using the implementation of the recommendations as a natural experiment.

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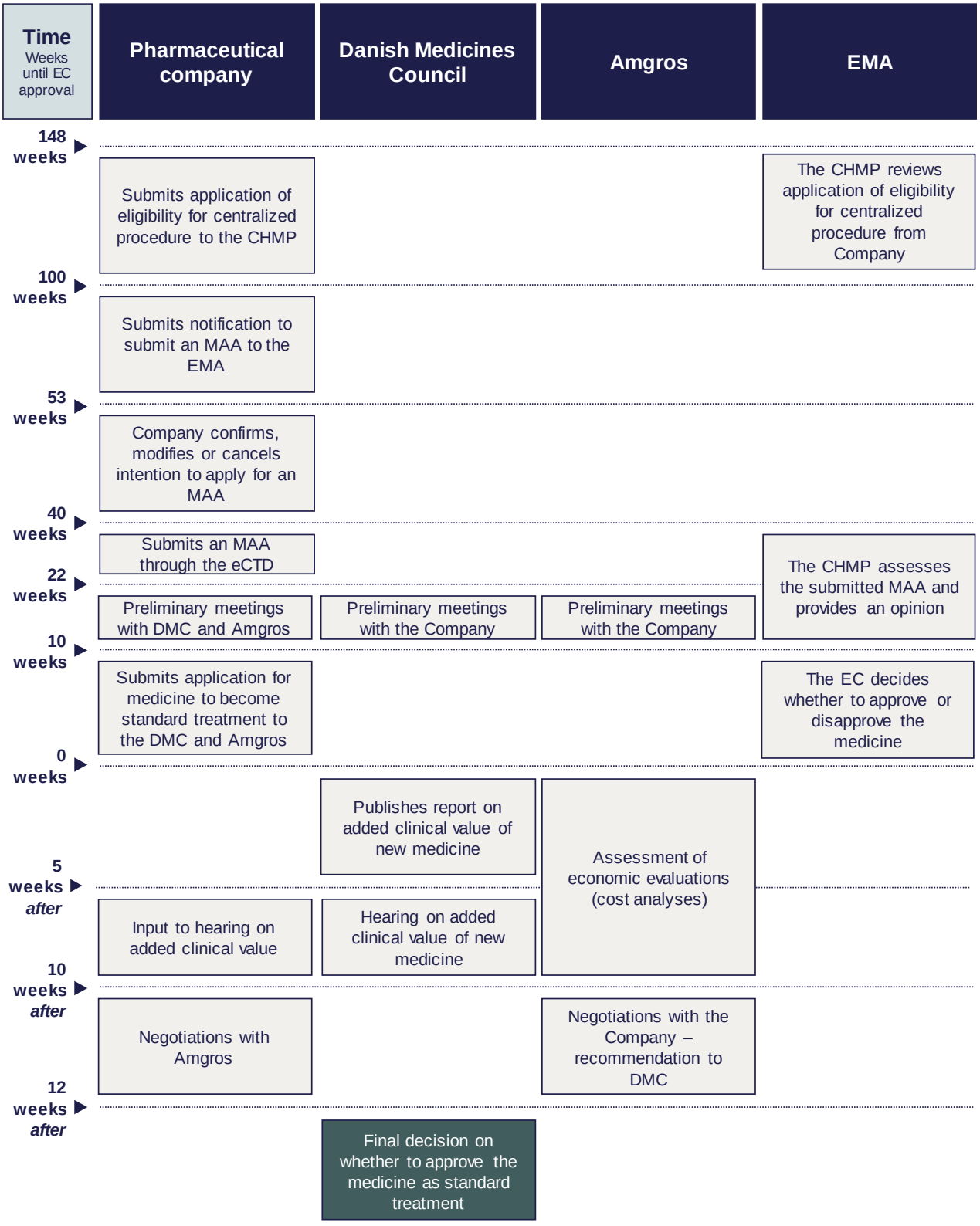
15 Appendices

15.1 Appendix A: Overview of introduction of a new hospital medicine



Source: Own construction, based on EMA (n.d.), Amgros (n.d.)

15.2 Appendix B: Overview of expert interviewees

Name:	Thomas Birk Andersen
Title:	Senior Consultant
Organization:	Danish Regions
Expertise:	Danish Public Healthcare Sector
Interview date:	01-03-2018

Description:

Works for Danish Regions as a senior consultant within center for health technology, business cooperation and regional development.

Name:	Ole Jannik Bjerrum
Title:	Professor Emeritus
Organization:	University of Copenhagen
Expertise:	Pharma & RWE
Interview date:	22-03-2018

Description:

Has been a professor of University of Copenhagen since 1988 in the field of Pharmacology.

Name:	Louise Broe
Title:	Chief Consultant
Organization:	The Danish Association of Pharmaceutical Industry
Expertise:	Danish Healthcare Sector
Interview date:	02-02-2018

Description:

Works as chief consultant at the Danish Association of Pharmaceutical Industry

Name:	Kalipso Chalkidou
Title:	Prof. global health, Director IDSI
Organization:	Imperial College
Expertise:	UK Healthcare Sector
Interview date:	25-04-2018

Description:

Works as the Director of Global Health Policy and a Senior Fellow at the Center for Global Development, based in London, and a Professor of Practice in Global Health at Imperial College London.

Name:	Jørgen Clausen
Title:	Chief Economist
Organization:	The Danish Association of Pharmaceutical Industry
Expertise:	Danish Healthcare Sector
Interview date:	02-02-2018

Description:

Works as the Chief Economist at the Danish Association of Pharmaceutical Industry.

Name:	Lone Due
Title:	Currently retired
Organization:	Capital Region of Denmark
Expertise:	Danish Public Healthcare Sector
Interview date:	22-03-2018

Description:

Currently retired. Previously worked at the capital region of Denmark. L.D. was responsible for providing guidance on medicine choices based cost-effectiveness to general practitioners

Name:	Afschin Gandjour
Title:	Prof. Dr. Dr.
Organization:	Frankfurt School of Finance & Management
Expertise:	Health Economics
Interview date:	05-04-2018

Description:

A.G. is a medical doctor, health economist, and philosopher. His research focuses on cost-effectiveness analysis, decision modeling, and value-based pricing of pharmaceuticals.

Name:	Dana Goldman
Title:	Professor
Organization:	University of Southern Carolina
Expertise:	Health Economics
Interview date:	12-04-2018

Description:

D.G. is director of USC Leonard D. Schaeffer Center for Health Policy and Economics and Prof. of Public Policy, Pharmacy, and Economics. D.G is adjunct prof. of health services and radiology at UCLA, and M.D. and founding partner of Precision Heath Economics.

Name:	Thomas Hedebye
Title:	Senior Advisor
Organization:	QVARTZ
Expertise:	Healthcare
Interview date:	23-03-2018

Description:

T.H. is a senior advisor of QVARTZ with expertise in healthcare. He has previously worked with healthcare in 6+ years for McKinsey & Company in New York.

Name:	Lene Hammer-Heimlich
Title:	Real-world Evidence Lead
Organization:	Lundbeck
Expertise:	Real-world evidence
Interview date:	13-03-2018

Description:

L.H. works as real-world evidence lead at Lundbeck. Has previously worked as epidemiology manager at Lundbeck, and has a Ph. D. in epidemiology from University of Copenhagen

Name:	Mikael Hilding
Title:	Engagement Partner
Organization:	QVARTZ
Expertise:	Healthcare
Interview date:	21-03-2018

Description:

M.H. works as an Engagement Partner at QVARTZ within healthcare.

Name:	Jakob Kjellberg
Title:	Professor, Course Leader
Organization:	VIVE
Expertise:	Danish Public Healthcare Sector
Interview date:	04-04-2018

Description:

J.K. has 15 years of experience within health technology appraisals. He aslo teaches courses within health economics, and has advised various Danish public healthcare institutions.

Name:	Torben Klein
Title:	Chief Executive Officer
Organization:	The Danish Medicines Council
Expertise:	Danish Public Healthcare Sector
Interview date:	22-03-2018

Description:

T.K. is the CEO of the DMC. He has previously worked as the Managing Director for the Novo Nordisk Foundation Center for Metabolic Research.

Name:	Henrik Ib Jørgensen
Title:	Chief Executive Officer
Organization:	Muscular Dystrophy Foundation
Expertise:	Danish Public Healthcare Sector
Interview date:	09-03-2018

Description:

Works as the CEO of the Danish Muscular Dystrophy Foundation and represents the patients' side.

Name:	Kjeld Møller Pedersen
Title:	Professor
Organization:	University of Southern Denmark
Expertise:	Health Economics
Interview date:	16-02-2018

Description:

K.M.P is prof. of the University of Southern Denmark and specializes in health economics.

Name:	Marianne Bork Samuelsen
Title:	Global Project Director
Organization:	Novo Nordisk
Expertise:	Real-world Evidence
Interview date:	22-03-2018

Description:

M.B.S. work as the Department and Global Project Director at Novo Nordisk. She has an expertise within RWE and regulatory affairs.

Name:	Flemming Sonne
Title:	Chief Executive Officer
Organization:	AMGROS
Expertise:	Danish Public Healthcare Sector
Interview date:	16-02-2018

Description:

F.S. is the CEO of AMGROS, and has had the position of 13 years.

Name:	Dorthe Eberhardt Søndergaard,
Title:	Department Head
Organization:	Ministry of Health
Expertise:	Danish Public Healthcare Sector
Interview date:	07-03-2018

Description:

D.E.S. works as the department head of the Ministry of Health. She has also participated in the price cap agreement.

Name:	Henrik Toft
Title:	Transformation Architect
Organization:	IBM
Expertise:	Real-world Data
Interview date:	09-03-2018

Description:

H.T. is a Transformation Architect at IBM.

Name:	Sigurd Vitols
Title:	Doctor
Organization:	Karolinska University Hospital
Expertise:	Healthcare
Interview date:	19-03-2018

Description:

S.V. is chef physician for the Karolinske University Hospital in Sweden.

15.3 Appendix C: Generic interview guide

Interview guide sample questions	
Question category	**Questions**
Pricing models	Defining a fair price for a medicine is often controversial. How would you define a fair price from payers' perspective? And from sellers' perspective?
	A fair price is, in this context, defined as one that optimizes patient access, payer affordability, and incentives for continued investment in research and development. What do you believe are the best pricing models in terms of supporting innovation for pharmaceutical companies, while at the same time offering payers a "fair" price?
	Under value-based pricing, what do you believe is the best method of measuring value?
	What do you perceive as the benefits and disadvantages of using value-based pricing?
	What countries do you believe have some of the best comprehensive pricing models?
	In your belief, can the price of a medicine be too high?
	What do you perceive as the benefits and disadvantages of using profit controls in medicine pricing?
	In your belief, should Denmark introduce QALY into cost-effectiveness evaluations, as it is used in the UK? If so, to what extent?
	What do you consider to be the weaknesses, if any, of the pricing model in the UK?
	To what extent should Denmark apply the same system as UK with QALY?
	What do you perceive as the benefits and disadvantages of using external reference pricing?

	Norway has since 2010 paid lower prices for medicines than Denmark. Do you believe Denmark should imitate some of the practices used in Norway?
	How would you describe the effectiveness of the Danish implementation of ERP? What are the main challenges?
Real-world evidence	To what extent do you believe that RWE can be used to measure the value of a medicine and determine a price? In your belief, should Denmark begin to use real-world evidence in medicine evaluations?
	In your belief, how developed are other countries at using real-world evidence in evaluating medicines?
	To what extent do you believe it would be possible to implement the use of real-world evidence in the Danish public healthcare system?
	Some academic articles note the challenge of using real-world evidence in practice due to a lack of clear-cut measurements of health developments. Do you agree with this critique? If so, is there a way to overcome this challenge?
	In your belief, what are the main obstacles to implementing the use of real-world evidence in Demark?
Danish public healthcare system	In your belief, is there public acceptance of the need to prioritize medicines in Denmark?
	In your belief, are the processes used to evaluate medicines by the Danish Medicines Council transparent?
	How can health technology appraisal organizations like the Danish Medicines Council improve transparency?
	How can public healthcare systems with limited medicine budgets accommodate the highly expensive, yet innovative new medicines?
	In your belief, can real-world evidence be used to mitigate the risk of overpaying for medicines in Denmark?
	How can new real-world data systems be implemented in Denmark? Can healthcare data records be centralized in the CPR?