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THE CHALLENGES OF ORPHAN DRUGS AND ASSOCIATED SOLUTIONS PROPOSED BY NORDIC HTA AGENCIES

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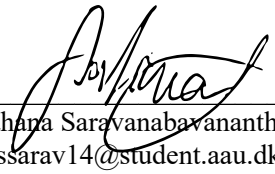

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ABSTRACT

Aim: The orphan drug market has become an attractive market for pharmaceutical companies but follows some challenges for societies around the world. In this relation, this thesis aimed to identify the challenges Nordic countries are facing with orphan drugs and the proposed solutions.

Method: Using seven individual interviews with HTA agencies in the Nordic countries (Denmark, Finland, Norway, and Sweden), the challenges faced during the assessment of orphan drugs and some solutions were identified. Furthermore, a collaborative process design was used to describe the tasks to be completed by the countries to establish effective collaboration between them.

Results: The interviews identified that the most prominent challenges concerning orphan drug assessment were high prices, uncertainty in evidence, and offset negotiation power. The countries use different solutions to overcome these challenges, and a proposed solution of cross-border collaboration is a possibility. The preliminary guideline, however, states that many elements have to be discussed among the countries to establish an effective collaboration.

Conclusion: This thesis confirms that much work must be done to find a definitive solution to overcome these challenges. Furthermore, most importantly, all stakeholders should be consulted for any solution to be adequate.

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RESUME

Formål: Markedet for orphan lægemidler er blevet attraktivt for medicinalindustrien, men medfører udfordringer for samfund rundt i verdenen. I den forbindelse var formålet med dette studie at identificere de udfordringer, som de nordiske lande står over for, når de vurderer orphan lægemidler, samt de foreslåede løsninger.

Metode: Ved hjælp af syv individuelle interviews med MTV-agenturer i de nordiske lande (Danmark, Finland, Norge og Sverige) blev udfordringer, i henhold til vurderingen af orphan lægemidler samt nogle løsninger identificeret. Derudover blev et samarbejdsproces design anvendt til at beskrive de trin, som bør følges for at etablere et effektivt samarbejde mellem disse fire lande.

Resultaterne: Interviewene viste, at de mest fremtrædende udfordringer i forbindelse med vurderingen af orphan lægemidler er høje priser, usikkerhed i dokumentationen samt misforhold i forhandlingsstyrke. Landene bruger forskellige løsninger for at overkomme disse udfordringer, og en foreslået løsning er tværsamarbejde mellem de nordiske lande. I den præliminære retningslinje findes frem til at mange elementer, som skal drøftes mellem landende, for at kunne etablere et effektivt samarbejde.

Konklusion Dette studie bekræfter, at en del forskning stadig skal udføres for at finde en definitiv løsning på disse udfordringer. Og vigtigst af alt bør alle interessenter konsulteres, så enhver løsning bliver effektiv, for alle parter.

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ABBREVIATION LIST

CHMP	Committee for Medicinal Products for Human Use
EC	European commission
EMA	European medicines agency
EU	European Union
HTA	Health technology assessment
MA	Market access
OMP	Orphan medicinal product
R&D	Research and development
RCT	Randomized controlled studies
RD	Rare disease
ROI	Return on investment
WTP	Willingness to pay

GLOSSARY LIST

Drug	In this thesis also referred to as, medicinal product, or medication
HTA agency	Are also referred to as, procurer
Nordic countries	Refers to Denmark, Finland, Norway, and Sweden
PEST	Political, economic, socio-cultural and technology
Quotes marked with *	Indicate that the quote has been translated from Danish to English by the author
Rare diseases	In this thesis, it refers to the EU's definition of a disease affecting 1 in 2000 in Europe
Seller	In this thesis also referred to as, the industry, pharmaceutical company, or manufacturer

1 INTRODUCTION

Rare diseases (RDs) are characterized as conditions affecting a small patient group with a prevalence of fewer than 2000 people in the European Union (EU), even though they affect an estimated 350 million people worldwide. Aside from the relative scarcity in population, RDs have no or limited treatment options, lack of resources, and are a significant disease burden. (1) In 2007 the estimated number of RDs in Europe was 5000 to 8000, affecting six to eight percent of the population, and only one percent is currently covered by approved treatment. (2) RDs are classified as rare as the prevalence of each disease is low. However, the number of orphan medicinal products (OMP) developed is increasing, and the burden imposed by the OMPs is both clinical and economic. As a result of the economic burden, the payers in the healthcare system are faced with the risk of turning down life-extending drugs and not responding to patients' needs. Consequently, the healthcare system is unable to guarantee equal access to treatment, and it faces enormous amounts of criticism from, among others, media, patient groups, and clinicians. This increment in the introduction of expensive drugs is beginning to threaten the sustainability of healthcare systems. (3,4) With low demand for each OMP, this market was neglected by the pharmaceutical industry due to the lack of profitability. An unmet need within this area of diseases was recognized by the EU, who aimed to incentivize manufacturers, both regulatory and economically, to develop OMPs, by passing legislation. (5) One of the existing economic incentives is the ten-year market exclusivity, which prevents other competitors from entering the market in this period. However, this impetus can pave the way for the development of market monopoly allowing manufacturers to charge immense prices for OMPs. (6) The average prices of OMPs, at market entry, have doubled every five years. Continuously, increasing prices are of particular concern for payers, as the prices might exceed their economic capacities. (7) The healthcare systems which are under growing pressure from scarce resources, aging populations, and high drug prices, can be tempted to reduce the emergence of expensive OMPs to balance their budgets. The extra costs posed by OMPs must be allocated from another place in society; however, as a consequence of the scarce resources, not all areas of healthcare can then be covered. (8,9) Given the budgetary constraints and apprehension of affordability, the price of OMPs can become a subject of matter on a societal level. (10)

2 BACKGROUND

2.1 HEALTHCARE MARKET

The traditional economic market is characterized by the trade of goods between buyers and sellers. This interaction between buyers' willingness to pay (WTP) and sellers' willingness to produce determines the price of a good, which also represents its value for both parties. The prices in healthcare markets are ascertained through negotiation or directly notified by the seller. The healthcare market is further framed by economic, structural, and social forces. This market structure was a response to rising healthcare costs. Accordingly, price competition theory is applied to healthcare, intending to constrain costs, increase efficiency, and make health providers more responsive to the priorities of payers, which is why buyer dominance became more prevalent than that of the health professional. (11,12)

Health is a nonmarket good as it cannot be exchanged between consumers; however, medicines are market goods aiming to improve the health of their consumers. Contrary to other goods, the consumption of medicine consists of uncertainty, as the benefit obtained is not immediate and can also be a result of the heterogeneous effect among patients. The buyer, payer, and consumer of this good are three separate parties. The consumer is the patient who pays for healthcare indirectly via, for example, taxes to the government. The government has the paying role aiming to obtain the highest health benefits for patients and simultaneously confining the healthcare costs within a predefined budget. Physicians act as the buyer, who prescribes medicine and is interested in improving the patient's health. Distinctively, price does not play a central role in regulating demand and supply, partly because the patient does not carry the full payment for healthcare. (13) This distinctiveness also indicates the extent the governments are involved in the healthcare market than in other markets. In this market, the government does not only act as a payer but also as a regulator. In perfect markets, interested buyers and sellers are left alone without any governmental involvement as the economic reason indicates that the market will lead to an optimal solution. Nonetheless, in the healthcare market, the conditions for a perfect market are rarely met as it is afflicted by market failure. The governmental regulations are present to pre-empt some market failures, such as information asymmetry, which is widespread in the healthcare market as various stakeholders have different knowledge about treatment. In traditional markets, there are more sellers and buyers of the same good, which is why the action of a single actor does not affect anyone. In contrast, there are only a few buyers and sellers in the healthcare market, for which reason the actors can perform market power. Market power enables

a seller to charge higher prices than in a perfectly competitive market. It can be created through different initiatives such as patent protection and market segmentation by which failure of competition arises, and the resulting consequence is high prices. This market power is also created by the national regulations in a country and the EU, especially during the market access (MA) process in the member states. (13)

2.2 Market access of pharmaceuticals in Europe

MA is comprised of regulatory entry barriers of a drug and the ability to access a market with a favorable recommendation. These barriers are marketing authorization, including pricing and reimbursement, logistics, and drug surveillance. The MA process is implemented to ensure that all patients, who would benefit from the treatment, get timely and continuous access at the right price. (14) The objective of the industry is to provide the broadest possible access to their drug. In contrast, the payer aims to restrict access to those patients who achieve the most benefits and gain the highest effectiveness and cost-efficiency. The industry has to convince the payer about the value of a drug, among others, to obtain access to a larger target population.

In each country, the rules for MA are outlined by a central agency. These rules involve criteria for funding decisions, and evidence requested for the assessment of products. In the European market, most drugs proceed through the centralized procedure that comprises of a single application from the company to the European Medicines Agency (EMA), where an EU-wide assessment and marketing authorization is granted. Member states apply to EMA to obtain centralized market authorization. The Committee for Medicinal Products for Human Use (CHMP) in EMA is in charge of the scientific assessment of applications and forwards the opinion on whether a drug can be authorized to the European Commission (EC). Based on the opinion from CHMP, the EC contemplate the legally binding decisions and can decide to issue a marketing authorization, valid in all member states. (15) The authorization is issued based on considerations of the product's safety, efficacy, and quality obtained from the highly controlled conditions of a randomized controlled trial (RCT).

Within publicly funded healthcare systems, found in most European countries, the government in each member state defines the overall purpose of public health and the corresponding funding for a drug, based on a predefined budget. (16,17)

2.2.1 THE ORPHAN DRUG MARKET

The MA for OMPs slightly differs from the non-OMP market on some counts, for instance, when it comes to access and legislation. Throughout the years, the EU has introduced legislation to incentivize the research and development (R&D) of OMPs. At the EU level, a drug can receive orphan designation based on Regulation Number 141/2000, which determines the procedure and criteria for these drugs. According to this regulation, the Committee for Orphan Medicinal Products within EMA is responsible for evaluating OMP applications. (18) However, to obtain this designation, the following criteria should be met:

- *Prevalence criterion* outlines that the drug should target diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions, which do not affect more than 5 in 10,000 in the EU when the decision is made (18)
- *Insufficient return on investment criterion* stipulates that the intended diagnosis, prevention or treatment of the disease would not generate sufficient return to justify the investment if it was not for the incentives also (18)
- *No satisfactory method criterion* describes that no other approach to diagnosis, prevention or treatment of the disease has been authorized (18)
- *Significant benefit criterion* is that the new drug demonstrates significant benefit over existing drugs for the patients (18)

Several incentives, both regulatory and economic, have also been established for the companies. These include protocol assistance, where the company can get guidance from EMA concerning different criteria and associated requirements to demonstrate the value of the drug during the centralized procedure by EMA. The free scientific advice for protocol assistance is granted to increase the quality of clinical trials and study protocols, thereby further prospect of a successful marketing authorization application. This guidance is of benefit for the company as there is usually a high level of uncertainty with the real efficacy of OMPs resulting from a low level of evidence available when launching the OMP. Furthermore, ten-year market exclusivity is granted, which provides the company with the benefit of protection against competition from similar products in the EU, with the same indication. From this benefit, three derogations exist; the company's consent to allow a second applicant, inability to supply, or if a similar product demonstrates a clinical superiority than the original OMP.

The incentives by the EU have encouraged the development of OMPs, for diseases that previously had no treatment options available. However, the market exclusivity has led to the creation of market monopolies, where the single company dominates the niche market. (18,19) Regulatory agencies

cannot approve a generic drug or brand name drug for the same RD indication during the marketing exclusivity period. The same drug can, withal, receive approval for a different disease indication, and currently, there are no limits on the number of drugs for the same RD profile. (19)

The resulting creation of a monopoly gives the monopolist power to decide the price. Opposed to this, healthcare payers have limited negotiation power, lack of information about the cost structure of OMPs, and are also pressured from patient associations to accommodate new OMPs. Patient associations promote healthcare payers to grant full reimbursement for the OMPs, regardless of their high prices. Consequently, the healthcare payers are often forced to accept the high prices which the manufacturers charge, or risk no access for patients in their country. (19,20)

2.2.1.1 Pricing

The pricing mechanism of OMPs is referred to as black-box pricing because of insufficient literature on these pricing mechanisms. The pricing is unique as the cost of R&D must be regained from a small number of patients; thus, higher prices are needed to obtain a sufficient return on investment (ROI). Pricing a patent drug is similar to monopoly pricing, consisting of price differentiation between different markets, because of diverse national conditions and regulations. Differentiating the price according to individual markets, the companies can maximize their profits by ensuring each buyer pays according to their willingness and ability to pay. The price differentiation between countries, and the following heterogeneous access to OMPs, can be caused by the given national budget constraints and associated political pressure. (11) An estimate suggests that cost per patient of OMPs is six times higher than that of non-OMPs, a clear indication of the industry's pricing power. The annual price of OMPs exceeds €100,000 per patient, while higher annual prices are observed for drugs with multiple indications. The higher WTP can cause these high prices due to the characteristics of the diseases and the limited treatment alternatives. Accordingly, the economic viability of certain OMPs can be questioned, as they have been proven to be effective in multiple diseases and thus having a larger target population. (19,21)

2.3 Current initiatives in the Nordic countries

Denmark and Norway have already established a contract in 2018, *Intensjonsavtale,* to collaborate on joint price negotiation and procurement on selected drugs. This contract is prepared in light of the introduction of new high-priced drugs, pressuring the budgets but also to oblige the critical supply of older drugs. The aim is to achieve access to the right drug at the right time and to the right price for patients and additionally ensure the security of supply. With this contract, the two countries want to

explore the advantages and disadvantages of a joint negotiation. In the beginning, the aim is to secure the supply of older drugs. With innovative drugs, the contract is expected to aim at OMPs, where high prices are expected. (22,23) Furthermore, FINOSE collaboration is established between Finland, Norway, and Sweden on joint procurement to ensure early access to drugs through a cooperative assessment. In this collaboration, the individual agencies are still in charge of reimbursement decisions in their own country. Currently, two joint assessment of non-OMPs have been conducted by this collaborative authority. (24)

3 PROBLEM STATEMENT

The previously disregarded market of orphan drugs has lately gotten increased attention from various stakeholders in societies around the world. This growing attention is induced by the incongruence of the pharmaceutical industry's proposed high prices and the HTA agencies' decision-making. The high prices of OMPs have prevailed since the introduction of regulations to incentivize treatment development to patients who otherwise have no available treatment options. Based on the current economic climate, OMPs might not be the economic exception they are now, given the pressure they currently, exert on national healthcare budgets. Furthermore, the growing budget impact of OMPs implies that an increasing share of limited drug expenditure is allocated to a few patients, challenging the boundaries of social solidarity. During decision-making, HTA agencies face a challenge with the trade-off between the opportunity cost of recommending a high-priced drug and limiting treatment accessibility for the patients' needs. The Nordic countries have tried to meet these challenges with various collaborative approaches, but the industry's preferences mainly manage these.

Accordingly, this thesis aims to identify and analyze the challenges regarding the decision-making of orphan drugs, which the HTA agencies in the four Nordic countries are facing during the assessment, as well as the negotiation process and describe different solutions. In order to answer the aim of this thesis, the following intermediate aims are compiled;

- Identify challenges faced by HTA agencies in Denmark, Norway, Finland, Sweden, and categorize the challenges according to the impact they have on HTA organizations.
- Identify the solutions which are currently implemented by the agencies and future solutions.
- Describe the attitude toward cross-border collaboration and the potential outcomes hereof.
- Outline a preliminary guideline for efficient cross-border collaboration.

To be able to answer the research question of this thesis, interviews will be used as a method to gather evidence, which will be analyzed based on various theoretical knowledge.

4 THEORIES

This section describes the various theories used to interpret the results obtained in this thesis. PEST analysis is convenient to identify and classify the challenges which the HTA agencies face. Moreover, the marketing and negotiation theories promote the understanding of the particular solutions identified and the market conditions within which the HTA agencies work.

4.1 PEST

PEST analysis is a strategic framework that enables analysis of external factors affecting an organization such as political, economic, socio-cultural, and technological. This analysis can aid an organization in identifying current and possible future challenges that, in return, equip them to plan ahead and manage these challenges proactively. By understanding the environment, there is a potential to maximize the opportunities and minimize the threats to an organization. The outcome of employing this tool is to help an organization to understand the market environment they are working in, strategically plan, and conduct market research in current and new markets. The assumption is that if an organization can audit its current environment and assess potential changes, it will be better positioned in responding to changes as moving into the future. (27, 28)

POLITICAL FACTORS

Political factors can be governmental policies, legislation changes, and political stability or instability to which the organization needs to respond. (27)

ECONOMIC FACTORS

Both macro- and micro-economic factors have a significant impact on an organization and its agenda. Economic factors can encompass demand in a market or budget constraints, which directly or indirectly can influence the financial performance of an organization. (27)

SOCIO-CULTURAL FACTORS

Socio-cultural factors have a direct effect on an organization's understanding of the demographics, values, beliefs, and in modern society, also media. When analyzing this factor, the organization becomes aware of the community norms to avoid violating these. (27)

TECHNOLOGICAL FACTORS

Technological advancements affect an organization and the management thereof. Planning to take advantage of technological developments could result in opportunities for growth. (27)

4.2 Marketing theories

4.2.1 Market demand

The law of demand states that if everything else remains equal, then the higher the price of a good, the lower the quantity of demand as the high price follows a higher opportunity cost of buying that good. When it comes to supply, the quantities are increasing at higher prices owing to increasing revenue. The interaction between supply and demand determines the price of a good. The price of a good can be affected by the price of a substitute, known as the substitution effect. When a financial difference occurs, a buyer might substitute a good with a lower-priced product. Another influential parameter is the income effect, where a buyer's income determines how much their ability to buy the product is. This means a buyer will purchase more of the good if the income is high and vice versa. These two effects together result in a downward sloping demand curve. Movement along the demand curve is caused by a change in the price of a good. In contrast, a shift in the curve is a result of a change in, for example, income. Monopolies face the market demand curve, and even if they increase the price, they will not lose all sales. As a consequence, monopolies set prices higher than the marginal cost to maximize profit. (28,29)

4.2.1.1 Price elasticity of demand

Price elasticity of demand is the responsiveness in demand due to changes in prices. If a good is inelastic, its demand does not change considerably with a change in its price. However, the demand of an elastic good varies due to changes in price. A higher inelasticity exists in a market without any substitute, which is the case for a monopolistic market. (30)

4.2.1.2 Buyer power

The buyer power is defined as the pressure buyers exert on sellers to provide, for instance, better prices. Various factors determine a high buyer power, such as a market with fewer buyers than sellers, price-sensitive buyers, and buyers who are well-informed of the product. In addition to this, buyers who purchase large quantities, and a market offering other substitutes do also contribute to high buyer power, as the buyer is not dependent on a particular seller. (31)

4.2.2 Price discrimination

Price discrimination is a strategy used by sellers to obtain the maximum price based on the assumption that specific market segments, value a good more than others and therefore are willing to pay more for that good.

This strategy is most beneficial when a seller's profit is higher under market segmentation compared to the one of a united market. The profitability and the price-setting depend on the elasticity of the market; in a highly inelastic market, the consumers are willing to pay a higher price. Sellers have an incentive to charge higher prices for a market segment with higher inelastic demand. A seller can operate as a discriminating monopoly as long as the price elasticity of demand varies among the consumers. (32) Not all sellers can price discriminate; they need to have market power. Without market power, a seller cannot charge above the market price. The consumers' demand curves are different from each other, which a seller must identify. Furthermore, the seller must be able to prevent the resale of the goods. (33)

There are three existing types of price discrimination; first-, second- and third-degree.

FIRST-DEGREE PRICE DISCRIMINATION

The first-degree discrimination is when the maximum possible price is charged for each unit. Thereby, the company secures all accessible consumer surplus-values. The price differs between consumers; therefore, some consumers might pay a higher price than others. (33)

SECOND-DEGREE PRICE DISCRIMINATION

Second-degree discrimination implies different pricing for different quantities, such as discounts when purchasing more than one unit. Volume discounts are an economic incentive to reduce unit prices for buyers who are buying large quantities. It is used by the seller to attract a buyer into buying larger volumes of the same product. (32, 34)

THIRD-DEGREE PRICE DISCRIMINATION

Third-degree price discrimination occurs when different prices are charged to different market segments. The marginal revenue of each market segment corresponds to the price and the price elasticity of demand in a particular market. (33)

4.3 INFORMATION ASYMMETRY

Information asymmetry comprises a situation where one party has a different level of information than the other, which gives rise to situations where the buyer's lack of information causes them to rely on, help from other parties to make decisions. The information asymmetry can be created under different circumstances and have different outcomes. In relation to price negotiation, the information concerning R&D costs of a medication can be asymmetric, as the seller has more information regarding the development of medication than the buyer. Buyers do not always know about what other

buyers are paying for the same product, and the seller has an incentive to keep these prices hidden because buyers pay more when they assume other buyers are paying the same. (11,33,35)

ADVERSE SELECTION

Adverse selection arises as a consequence of opportunistic behavior from asymmetric information. The problem emerges when one party to a transaction possesses information about hidden characteristics that are unknown to other parties and takes economic advantage of this information. Adverse selection may prevent beneficial transactions from occurring. (33)

4.4 NEGOTIATION

4.4.1 INFLUENCE TACTICS

Negotiators use different tactics to influence their opposite party to comply with their request to obtain maximum benefits. It is suggested that the power of a negotiator is expressed in the degree of influence capacity when using influence tactics. In this relation, nine dimensions of influence tactics are used. One of them is ***pressure,*** which can be in the form of threats, demands or intimidation of the opposite party. In contrast, some negotiators use ***legitimation*** by finding grounds to legitimize the request or by claiming the right to request compliance by referring to an existing policy. ***Exchange*** is when a party makes an implicit or explicit promise to reciprocate if the opposite party complies. In a negotiation process, the negotiating parties can use the assistance of others to help persuade or pressure the opposite party to comply, which is known as ***coalition.*** The negotiators not only apply tactics that push the opposite party to comply but also attempt to make a favorable impression and improve the opposite party's mood before requesting (***Ingratiation***). One of the most well-reputed persuasion tactics is the ***rational persuasion,*** as it is the use of logical arguments and factual information to support the viability of complying with the request. Contrary, the ***inspirational appeal*** is directed to emotions by targeting the values and ideas of the opposite party, as emotions are seen as the primary drivers of motivation. ***Consultation*** is seeking the opposite party's participation in the decision-making process and the implementation of the request. When consulting the opposite party, it commits them to the request making them feel involved, which follows motivation to take action to ensure compliance with the request. ***Personal appeal*** is the appeal to the opposite party's sense of loyalty or relationship prior to requesting. (36,37)

5 METHOD

5.1 INTERVIEW

In order to answer the research question of this present thesis, seven semi-structured, one-on-one interviews were conducted using Skype as a platform to interact with the respondents from Denmark, Finland, Norway, and Sweden. The interviews were completed in the period from March 11th, 2020, to April 30th, 2020.

5.1.1 METHOD

This thesis aimed to examine the HTA agencies' challenges with OMPs, why interviews were deemed appropriate as they enable access to respondents' work with OMPs. An interview is a great method to obtain detailed information, in respondents' own words, about personal opinions and experiences. The application of interviews gave the present thesis access to unique primary data, which would otherwise have been challenging to address.

The type of interview chosen in this thesis was a semi-structured interview with a pre-planned interview guide containing the overall questions related to the focus of research, as seen in Appendix 1.A and 1.B. The semi-structured form was adopted as there was no explicit sequence of questioning and more perceptiveness to understand the respondents' perspectives was needed in the beginning. The respondents had the opportunity to take the interview in other directions to uncover new perspectives of the research. During the interviews, it was possible to add supplemental questions whenever an interesting point of view came up, resulting in the acquisition of more specific and distinctive evidence. The pre-planned interview guide facilitated a similar type of data collection across the respondents and kept them from discussing topics unrelated and irrelevant to the research.

Six out of seven interviews were one-on-one, permitting more in-depth insight because more detailed follow-up questions were asked. As the aim of this thesis presented some politically sensitive questions for some people in the healthcare industry, the one-on-one interview created a more open setting for the individual respondents to be candid and open up. In one of the interviews, two respondents participated together.

5.1.2 RESPONDENTS AND SETTING

The respondents were recruited by addressing respective employees from HTA agencies in Denmark, Finland, Norway, and Sweden via e-mail. The only inclusion criteria applied for the respondents was

that they were employees from HTA agencies in these four countries, working with drug assessment processes. These recruitment e-mails were sent to the employees on March 3, 2020, in which the respondents were requested to participate in an interview between March 11, 2020, and May 15, 2020.

The employees who accepted this request were sent a declaration of consent concerning audio recording, transcription, and anonymization of the interview, as found in Appendix 2.A and 2.B. Prior to the interviews, the respondents signed the written consent and thus agreed to voluntarily participate in an interview. The decision to anonymize the respondents was to accommodate any hesitancy there might be to answer any sensitive questions and to construct a safer environment where the respondents' answers could not be personally associated with them. The only information about the respondents sustained in the interviews was the country to which the respondent belonged. This information was considered essential to understanding the different perspectives presented by the respondents, the restrictions to their knowledge to answer the questions, and their working environment.

The platform in which six out of seven interviews were conducted was Skype to reach the long-distance respondents. A considerable amount of convenience was related to the use of Skype as an interviewing platform. The respondents could situate themselves in a comfortable and suitable place to promote a relaxed environment for the interview. The time frame for these interviews lasted from 25 to 35 minutes as the respondents had a busy work schedule, and this time frame was set when recruiting the respondents.

The interviews with respondents from Denmark were conducted in Danish to comply with the respondents' comfortability and allowing them to express themselves more freely in their native language, which eliminated the language barrier between the researcher and the respondent. The rest of the interviews with respondents from Finland, Norway, and Sweden were performed in English.

One of the interviews was conducted by e-mail, which made the interview asynchronous as the respondent answered the questions according to openings in their schedule. The questions from the interview guide were sent to the respondent, who replied to the questions as he/she had time. The flexibility in the e-mail interview made it possible to access the respondent who had a busy work schedule. Follow-up questions were sent to the respondent after receiving the first set of answers.

5.1.3 Data collection

In order to efficiently collect data, the pre-planned interview guide was constructed on a mix of grand-tour and mini-tour questions. All interviews began with a grand-tour question of how the process of

OMP assessment progressed in the respondent's country. Opening with a grand-tour question enabled the respondents to explain their work with OMPs, including focused details, which opened up for interesting new views for further investigation. Mostly, this followed mini-tour follow-up questions to gather a more detailed description of the statements of interest. Not every interview got through all questions from the interview guide, as the respondents answered differently, each expressing various interesting views. Following the first interview, additional questions were added to the interview guide because distinctive points were revealed along the way, which were of interest to this thesis.
Prior to one of the interviews, a respondent requested the interview guide to assess whether the questions were regarding confidential information giving the respondent an insight into the course of the interview. It was chosen to pre-send the questions to secure respondents' comfort even though aware of the bias this could bring to the interview.
Audio recordings were used to save the data from the interviews performed via Skype, making it possible to relisten to the conversation subsequently. By recording the whole conversation, it was possible to concentrate entirely on the respondents' replies and not miss any information for further elaboration. Despite video recording being an option, audio recording was chosen as the purpose of this interview was to analyze the statements and experience of the respondents for which video was not necessary.
Based on the audio records, the interviews were transcribed manually on a computer, where the onomatopoeic words, such as *'er'* and *'hmm'*, were excluded from the transcripts, due to irrelevance in relation to the further analysis. Silence, in the middle of a reply, was marked with *'(...)'*, and to respect the anonymization of the respondents, their job titles were anonymized as '*JT*" in the transcripts. During one interview, the internet connection was of poor quality, which resulted in the loss of some information. The transcript was subsequently sent to the respective respondent to skim and check whether any information was missing.
The spoken language in the interviews was transcribed directly in the transcriptions, as seen in Appendix 3.A through 3.G. The quotes, from the transcripts, used to support the analysis, were rewritten in written language to promote understanding of what was expressed, even though aware of the decrement in validity this brought.

5.1.4 Data analysis

The analytical approach used to analyze the transcriptions was thematic analysis, as this was useful for highlighting similarities and differences between the respondents' perspectives and summarizing

key features in the large dataset. The analysis was conducted to develop meanings of the interviews combined with the respondents' understanding, as well as providing new perspectives to the research. The transcripts from the interviews were analyzed in Nvivo to identify different challenges with OMPs, solutions for these challenges, and the general attitude toward Nordic collaboration. The transcripts contained a wide range of unstructured data, coded by initial coding based on the respondents' statements, as seen in Appendix 4. The coding was addressed deductively, as some of the codes were described in advance, as these emerged during the interviews. By using a deductive approach, it initially gave the unstructured data more structure. Hereafter some additional codes were added to the analysis, and the transition to a more inductive approach contributed with more in-depth analysis.

The initial codes accentuated the central themes and ideas expressed by the respondents. Subsequently, the transcripts were reread to find the connection between the codes to then categorize those with the same theme.

Following the initial coding broader categories were identified relating the codes to each other; here, four themes appeared: *'Challenges faced by the HTA agencies regarding orphan drugs', 'Strategies of pharmaceutical companies, 'Current and proposed solutions',* and *'Collaboration as a solution'*. During the interviews, some of these themes were identified, so the coding of analysis was initially deductive. However, it became more inductive when the transcripts were analyzed further, and new themes with relevancy to this thesis appeared. As the codes were categorized into these broader categories, some of the coding fitted more than one category.

The analysis was an iterative process as there was a continuous interplay between data collection and analysis. The interview questions changed based on the analysis made in the prior interview. As mentioned, additional questions to the interview guide were added based on interesting statements appearing in the previous interview.

In order to understand the results of the analysis, various theories were used. The theoretical knowledge recontextualized the themes to a universal sphere, providing a deeper understanding of the respondents' perspectives.

5.1.4.1 Theories

In this thesis, the general theories were applied to interpret the results. PEST analysis was used to interpret the external and internal challenges faced by HTA agencies when working with OMPs. This analysis was a preferred tool as it gave a perspective on which factors influenced the HTA agencies regarding OMPs and what impact they had on these organizations. As the tool is a strategic planning

method, it was convenient to analyze the challenges because this analysis provided details about the operating challenges in HTA agencies' macro environment and the impact these factors had on the organizations. It audited the organizations' environmental influences to use this information to guide strategic decision-making.

The marketing theories were used to obtain a better understanding of the interaction between the industry and the HTA agencies. These theories were based on the procurers' perspective since this thesis was conducted from the perspective of the HTA agencies. The theories facilitated the explanation of how some of the solutions proposed by the respondents was theoretically valuable. Together with the marketing theories, the theories behind influence tactics were employed to investigate the purpose of various strategies that were used by the pharmaceutical companies. With the use of these theories, it was possible to understand the mechanisms in a market where the HTA agencies interact with pharmaceutical companies and the intention behind the strategies. Furthermore, it enabled an understanding of how practical the solutions proposed by the respondents were in the presence of these strategies.

5.2 COLLABORATIVE PROCESS DESIGN

In order to outline a preliminary guideline for the HTA agencies to follow if they chose to collaborate, a collaborative process design by Institute for Coalition Building (38) was used. This tool was useful for summarizing the central elements from the interviews to lay out the challenges, solutions, and expected outcomes of cross-border collaboration between Denmark, Finland, Norway, and Sweden. By using the responses from the interviews to outline the process and steps for consideration, the basic planning of collaboration was made. Four areas were reflected upon; 'who', 'why', 'what', and 'how'. The 'who' included the people to consider engaging in collaboration, such as the partners and the stakeholders. In contrast, the 'why' considered the purpose and expected outcome of a collaboration, which was determined to be the same as most respondents indicated in the *'advantage of collaboration'*. The 'what' examined elements that could not be addressed as a single organization but by a collaborative organization, also seen in the *'advantage of collaboration'*. The 'how' was managed in the *'barriers to overcome'*, as these indicated which factors should be prioritized when planning the process in order to obtain a successful collaboration. Some of these areas were covered in the interviews, whereas others were proposed to the HTA agencies as tasks to complete.

6 ANALYSIS

6.1 INTERVIEW

The following sections analyze and interpret the four main themes; Challenges faced by the HTA agencies regarding orphan drugs, strategies of pharmaceutical companies, current and proposed solutions, and collaboration as a solution. It should be noted that even though the challenges identified are diverse, they are interrelated. Some of the issues are special for RDs, whereas others also apply to common diseases.

6.1.1 CHALLENGES FACED BY THE HTA AGENCIES REGARDING ORPHAN DRUGS

In the conducted interviews with HTA agencies in Denmark, Finland, Norway, and Sweden, different challenges regarding OMPs were outlined. These challenges are emerging from various external factors, such as political, economic, socio-cultural, or technological. With the PEST analysis, the current challenges are identified and classified according to their external origins and what menace they pose to society.

POLITICAL

The HTA agencies are facing challenges due to political pressure, which drives the decision-making in a particular direction.

POLITICAL PRESSURE

Agencies need to respond to governmental interference in the decision-making process, which is particular in the case of OMPs. Across the seven respondents, the political significance is made explicit, but DK1 is the only respondent who expresses the unwritten pressure from politicians regarding OMPs *(Appendix 3.C p. 6, l. 21-25).* The concern is conveyed in continuation of a discussion regarding equitability across diseases. The governmental influence attempting to pre-empt possible market failure and promote equitability is regarded as a pressure to give OMPs special treatment.

During the review of solutions to accommodate the high prices for OMPs, a different aspect of political pressure being a challenge manifest itself, which is seen in the following quote;

"*I think many of the rules that we have in the Medical Council now, such as doing a recommendation within 12 weeks, which makes us one of the quickest countries to make a recommendation. It's a political pressure from the pharmaceutical industry. Not to be blind to the fact that they want to ensure they get some really good prices in Denmark. If you have to be the quickest country and one*

*of the first countries to make a recommendation, then that's not where they are willing to lower the price" * (Appendix 3.C p. 10, l. 5-10).*

The outcome of this challenge is that Denmark is not guaranteed lower prices if they also have to be the first country to make a recommendation. The political influence is at the expense of an economic challenge for society, according to DK1.

ECONOMIC

The economic challenges mainly consist of microeconomic factors, as the respondents are faced with high prices and different company pricings of OMPs, in the presence of budget constraints.

HIGH PRICES

Following a question of the primary concern when working with OMPs, most respondents' answer is the high prices proposed by the industry. The high prices for OMPs are accompanied by implications of the decision to allocate resources among diseases, which concern the respondents about sustainability. This is expressed by SE1; *"Because prices are now unreasonable, and affordability will go out of hand for a lot of countries" (Appendix 3.B p. 5, l. 31-32).* In light of scarce resources in society, high prices pose a threat to economic sustainability. As these drugs are meant for a small patient group, it entails that a large share of the scarce resources has to be allocated to these patients. There is a consensus, that equity among patients should be appraised, which makes it difficult to say no to treatment for these patients, leading to economic sustainability issues.

UNKNOWN PRICES AND RESEARCH AND DEVELOPMENT COSTS

Another economic factor that is challenging for procurers is the fact that R&D costs are unknown to them. NO2 answers to the questions regarding solutions for high prices; *"Since we don't know the research and development cost, it is hard for us to really say whether the price is too high or too low" (Appendix 3.F p. 6, l. 20-22).* The procurers' ignorance of R&D costs makes it difficult for them to assess a righteous price for a drug. The information asymmetry arising in this situation can cause adverse selection as it is unknown to the procurer whether the price reflects the investment costs.

Furthermore, there is a broad agreement between the respondents that the confidential pricing agreements between HTA agencies and the industry, present a challenge to pricing in the individual countries. This concern is seen in the following quotation by FI2*; "Furthermore, the often significant, difference between list prices and negotiated prices may somewhat obscure the situation (...)" (Appendix 3.E p. 2, l. 14-16),* replying to a question regarding issues with OMP pricing. NO2 also agrees

to this and adds that it is difficult to estimate a reasonable price if the price from other countries is confidential *(Appendix 3.F p. 5 l. 18-19)*. The confidentiality results in a buyer who is not well-informed about the price ranges among other buyers weakens the buyer power and challenge them in negotiations, as there are no prices of reference.

SOCIO-CULTURAL

The socio-cultural factors influencing HTA agencies are the impact of media and organizations, and the market size affecting the power dynamic between industry and procurer.

MEDIA AND ORGANIZATIONS

Media and patient organizations impact decision-making by pressuring the negotiators. Patient organizations represent the patient demographic and their values, which should be taken into consideration by the procurers during decision-making. SE1 replies to a question about the power of patient organizations that these play a role in pressuring the buyer during negotiations *(Appendix 3.B p. 7, l. 19-21)*. Media is a socio-cultural channel allotting attention to cases and making them a matter of society. The pressure from media puts the case into a perspective that benefits one party over another. When answering the question about OMP assessment DK1 expresses how this is influenced by media; *"After all, these are the types of cases that come to the media where people say you are bestial about orphan drugs then it's unreasonable to assess them on the same level as with all sorts of other drugs. But it is not because it's orphan but because it's severe diseases "(...) * (Appendix 3.C p. 3, l. 23-26)*. In this quote, it is underlined that the value of the media is the severity of diseases and not a rarity, which reflects society's values. However, DK2 reason that this pressure is passed on to the manufacturers with the argument to reconsider their proposed prices *(Appendix 3.G p. 6, l. 16-20)*. Thus, not all the respondents feel pressured by media to make particular decisions regarding reimbursement.

MARKET SIZE

In continuation of discussing power in negotiations, DK1 mentions that the Danish market is a small market, which makes it difficult for them to drive down the prices in negotiations *(Appendix 3.C p. 9, l. 27-31)*. The market size and thereby, the population size in each of the Nordic countries have an impact on the negotiation, whether it is positive or negative. The socio-cultural characteristics in a country can determine the prices or be a reason for the negotiated prices in each country, as it among others, reflect the heterogeneous nature of RDs. Other respondents agree that the market size

influences buyer power in a negotiation. However, as Denmark is one of the smaller markets, it is more of their concern than the other Nordic countries'.

TECHNOLOGY

The new medicines for RDs are considered technological developments, and the lack of knowledge and evidence regarding these drugs present challenges to the HTA agencies.

EVIDENCE BASE

The evidence submitted for OMP assessment is found challenging by every respondent. It makes it difficult for most respondents to assess OMPs with the same methods as for non-OMPs, for which reason the effect is also challenging to evaluate. This is experienced regardless of the protocol assistance the manufacturer obtains by EMA when a drug is orphan designated. The frequently mentioned issues concerning lack of evidence, are small trials and high uncertainty. FI2 mentions that the high prices which are suggested by the pharmaceutical companies are difficult to be justified by the limited clinical evidence available *(Appendix 3.E p. 2, l. 14-16)*. Along with the lacking clinical evidence, the understanding of RDs' pathogenesis is also inadequate according to NO1, as seen in this quote;

"And obviously there can be a problem there as well measuring QALYs because of two things. One is that there are often little findings from literature while in ordinary diseases there are a lot of literature on the QALYs so we have more data we can compare with and we can choose from but, and this is for all of orphan diseases, it could be difficult to find what is really important because there is a lack of understanding of the diseases. If the disease is very rare it could be that we don't really know the mechanisms in the disease which makes it difficult to get input from clinicians and so forth" (Appendix 3.A p. 2, l. 16-23).

This quote suggests that uncertainty in evidence arises, as the drug's effectiveness cannot be measured due to poor understanding of RDs. Furthermore, DK2 confirms that the uncertainty in evidence is reflected in the price negotiation, as this cannot support the categorization of the surplus-value of the drug. The Danish HTA agency is challenged to associate the expensive drug with surplus-value, resulting in difficulties in estimating a suitable price range *(Appendix 3.G p. 2, l. 11-17)*. This challenge is present regardless of the methodology used in the four countries, as both Denmark and Norway experience this. The HTA agencies do not have any strong evidential support to decide in either a negative or positive direction, regarding reimbursement.

NO ALTERNATIVE

The lack of other alternatives for the RD patients is reflected in the decision-making for the HTA agencies. This lack of technological development in the country is an added complication that gives payers in the country no option but to purchase the drug regardless of price *(Appendix 3.B p. 6, l. 9-12).* The lack of alternative treatment combined with the market exclusivity, provided to OMPs, lead to OMP manufacturers facing the market demand. In the monopolistic market, the manufacturer becomes price-setters, and thus, the agencies find themselves in a predicament in which they are required to make decisions to ensure equal access to treatment for patients in their country while simultaneously juggling affordability.

Various challenges are identified in the interviews, some of them are wide-ranging, and others are reserved for some countries. Even though these are categorized according to the challenging factor they pose in decision-making processes, they are all interrelated. The most prominent factors challenging the HTA agencies are *'economic'* and *'evidence base'* as these combined characterize the main issue of OMPs. The political and socio-cultural factors pressure HTA agencies to make particular decisions regarding OMPs, while the technological growth and lack thereof add to this pressure. The Nordic HTA agencies are wedged in between affordability and securing their patients' treatment.

6.1.2 STRATEGIES OF PHARMACEUTICAL COMPANIES

The pharmaceutical companies use different strategies when interacting with HTA agencies, which can explain some of the challenges mentioned in section 6.1.1. The strategies are identified and analyzed by applying marketing theories, influence tactics, and how they might explain the challenges faced by the HTA agencies.

USE OF POLITICS

Governmental interference in healthcare systems is evidential as the respondents describe the challenge of political influence on decision-making. According to DK1, the pharmaceutical industry uses political pressure for the assessment process to be fast *(Appendix 3.C p. 10, l. 5-10)*, as referred to previously. The advantage arises for the pharmaceutical companies to charge higher prices in Denmark as they are among the first countries to recommend the drug. If the pharmaceutical companies set a low price initially they cannot set a higher price for the subsequent countries. However, this is

not in compliance with the challenge of confidential pricing; the other countries are unaware of the Danish prices and cannot use reference pricing to obtain lower discount prices.

PRICING CONFIDENTIALITY

The challenge to estimate prices due to price confidentiality among countries is seen as a strategy from the pharmaceutical companies to obtain maximum prices from each country. The companies argue that confidentiality is needed to give the respective countries the biggest discounts. According to NO2 it is difficult to assess whether this is true and whether the price is higher than in other countries *(Appendix 3.F p. 5, l. 19-21).* Generally, this is a wide-known issue among the four HTA agencies.

Price confidentiality is a way for the industry to maintain information asymmetry to preserve price discrimination, and through which they can obtain the highest price from each market segment. The information asymmetry provides companies with a higher power in negotiation. Furthermore, the influence tactic of exchange is also playing a role here, as the industry promises considerable discounts and, in return, expects the confidentiality of prices. They use these confidential prices to persuade one country about finalizing a price based on the recommendation in another country, which is why adverse selection occurs. The companies take economic advantage of the knowledge only they possess. NO2 describes this persuasion in this quote; *"But the companies will come to us and say hey NICE has evaluated our drug and it is a positive evaluation. But then we say, but we don't know the price openly" (Appendix 3.F p.5, l. 14-15).* The influence tactics used here is rational persuasion and coalition. By using NICE as a reference, Norway is persuaded to decide on the fact that NICE has made a positive recommendation. Even though NICE does not directly interfere in this situation, the coalition forms when the industry uses NICE as a reference to encourage compliance to the industry's request.

UNCHARTED RESEARCH AND DEVELOPMENT COST

The cost of R&D is also unknown for the HTA agencies and is outlined by the respondents as a challenge. According to NO1, this is a strategy which companies apply: *"I don't believe that the prices are set based on resource used for R&D. I think they are based on trying to extract the most they can from each country" (Appendix 3.A p. 5, l. 10-11).* NO1 expresses this to answer the question regarding solutions for OMP price reduction. The companies have information about the R&D, which is not shared with the procurers, and information asymmetry is used for the companies' benefit. The

manufacturers exploits this information to drive up the price for their drug, which is supported by a statement from SE1: *"(...) the other problem is that when we make our assessments and even when we for the very first time say we will increase or double willingness to pay, then the company says that's still not high enough" (Appendix 3.B p. 3, l. 7-10).* As the WTP loft is raised, companies try to leverage a bit more to see if the procurers are willing to go higher on the price.

Since the R&D costs are unknown for the HTA agencies, this information asymmetry is used for the companies' advantage to rationally persuade the HTA agencies to comply with the request of a price. Rational persuasion is based on the fact that manufacturers argue that the expensive cost of R&D need to be recouped from a few patients *(Appendix 3.C p. 7, l. 27-29).* When looking at the law of demand, the higher the price, the lower the demand. Since the pharmaceutical companies beforehand know that the demand will be low, they tend to set the price high to redeem the investment. Even though the company faces a monopoly demand curve, it only has a few patients, resulting in low demand. Furthermore, an adverse selection also emerges as the HTA agencies are unaware of the real costs and can end up paying more than the real value of the product.

MARKET SEGMENTS

The pharmaceutical companies have an incentive to divide the markets to obtain better prices, based on the different WTP in each country. DK1 mentions the market division as an obstacle, in relation to a discussion of existing co-operation agreements, since companies achieve higher profits by negotiating individually *(Appendix 3.C p. 11, l. 13-14).* All respondents touch on this controversy when asked about obstacles with a united market. This strategy is third-degree price discrimination as the industry segments the markets by country and charge different prices for each country. By doing so, the industry acquires the maximum price from each country according to the different demand elasticities. The establishment of market segments paves the way for price confidentiality and the use of positive recommendations in one country, to rationally persuade other countries to make the same decision.

MEDIA

As mentioned before, the media possesses high power, to the extent that the HTA agencies consider it a channel presenting challenges. Additionally, HTA agencies believe that companies use media to build up their power. This is expressed as a concern by NO1 when asked about solutions to price reduction: *"I think that in many of these cases the companies try to build up a negotiation power*

through media with case-studies in media and, so forth. And ultimately, you feel very sorry for these patients that have these rare diseases obviously" (Appendix 3.A p. 5, l. 4-6). The media create sympathy for these patients and portray the HTA agencies as the bad guys, when not granting a positive recommendation for a particular drug. The influence tactics used in this strategy are both pressure and inspirational appeal. The pressure tactic consists of the indirect pressure placed on the HTA agencies from the industry through the media. In contrast, this pressure is in form of inspirational appeal by appealing to the emotions when referring to the need of the patients. The media acts as an assistant to pressure the decision-makers, for which reason coalition tactic is also used in this strategy.

ZERO COMPETITION

The companies which have an orphan designation for their drug, most likely, do not have any competitors in the market for the same indication, which gives them a position as the price-setters. The position in a market obtained with orphan designation give the company power to set high prices *(Appendix 3.B p. 6, l. 9-12).* The challenge known as *'no alternative'* adds to the companies' power position as the procurer cannot provide any other treatments for their patients. The market demand is the demand for the company's drug, as no substitutions are available to shift the power from the seller to the buyer.

The fact that there are no alternative treatments pose as an indirect inspirational appeal, as the need for the patients has to be taken into consideration when making decision regarding the only available treatment. With EMA's orphan designation, the companies can legitimize their drug as being indispensable when negotiating to influence HTA agencies. The underlying criteria in EMA to obtain orphan designation becomes supporting evidence for the exclusivity of the drug for these patients.

The respondents present different suggestions to what strategies the industry might be using when it comes to OMPs. Primarily, the respondents agree that the industry uses information asymmetry to maximize their profit in each market segment, which is also reflected in the expressed challenges.

6.1.3 CURRENT AND PROPOSED SOLUTIONS

In the interviews, the respondents accentuate some of the initiatives and methods they have implemented in their country to overcome the challenges presented by OMPs and to accommodate the strategies from manufacturers. Additionally, the respondents suggest other solutions, which they

consider effective in this setting. In this section, these solutions are categorized into current and proposed solutions, including collaboration, and described in relation to the respondents' statements.

6.1.3.1 CURRENT SOLUTIONS

ALTERNATIVE DATA

The nature of RDs and the aforementioned challenge regarding uncertain evidence pushes the HTA agencies to search for alternative data. DK1 mentions that they look at existing treatment alternatives and draw on knowledge from the particular RD area to obtain more data. In terms of assessing the effectiveness of a new OMP, the Danish Medical council leans on this new insight *(Appendix 3.C p. 2, l. 24-27).* By looking into the disease area, the procurers obtain more knowledge about the benefits the new OMP might bring the patients and even some of the information asymmetry, in order to strengthen their power.

OTHER DECISION PARAMETERS AND CRITERIA

Drawing on other decision parameters or criteria is also a way for the HTA agencies to overcome the lack of evidence. Most of the HTA agencies are more permissive with data when it comes to OMPs. Norway, for example, accepts a lower quality of data, because they know that evidence is sparse in RDs *(Appendix 3.A p. 1, l. 18-20).* However, Norway does not utilize any particular criteria when assessing OMPs, but based on the severity of the disease, they allow an elevated WTP *(Appendix 3.F p. 3, l. 3-6).* The elevated WTP for OMPs is, generally, employed by the four HTA agencies, according to the severity of the disease.

A commonly used criterion applied in assessment is severity, which the four countries use based on different premises. Additionally, Sweden has three criteria they use to assess new drugs, as seen in this quote;

"(…) the three criteria we have are the same for everything, so the principle of equal human value. Then the second one is need and solidarity, which says that we shall pay more for the once with the more severe conditions, but it doesn't say how much more. And the third criterion is the cost-effectiveness, telling us to preferably buy those treatments, that give the best value for money" (Appendix 3.B p. 2, l. 19-22).

These three criteria are applied to all new drugs and make the assessment process for all drugs equal. Finland also uses some similar criteria as Sweden but considers rarity of the disease, as well *(Appendix 3.E p. 1, 13-15).*

Each country uses different criteria when considering the value of drugs, instead of solely assessing clinical effectiveness and cost-effectiveness. These criteria establish values that the drugs have to comply with to be recommended, which in turn increases the buyer's power.

METHODOLOGICAL APPROACHES

In general, the methodological approach in the four countries differs, as Denmark does not use a QALY model. However, NO2 thinks that the method used in Denmark, to value a drug, is an effective solution *(Appendix 3.F p. 7, l. 7-11).* Denmark categorizes the drugs according to their surplus-value, which can be an advantage, considering the high uncertainty in evidence, however DK2 mentions that the uncertainty is also challenging in order to assign the effect a surplus-value *(Appendix 3.G p.2, l. 12-18).*

As previously indicated, some of the countries consider rarity and severity, which are sometimes not distinguished between. Norway uses a methodology to quantify the severity; *"For severity we use something called absolute shortfall. Which is a method of quantifying the QALYs due to disease compared with the same normal population*" *(Appendix 3.A p. 3, l. 10-12).* By using this comparison, Norway assures to assess the new OMP according to its severity, as they quantify the QALYs lost due to disease. The absolute shortfall is a method, of separating severity from the rarity and use this as evidence to legitimize the HTA agencies' price request, when negotiating.

FOLLOW-UP

High prices and high uncertainty in evidence make it difficult for HTA agencies to limit the costs to patients with proven effectiveness. Norway deals with this issue, by the doctors following up on patients based on start- and stop criteria, after administering patients the new drug *(Appendix 3.A p. 4, l. 24-28).* The application of these start- and stop criteria, constrict the treatment to patients with a measurable effect, and limit the expense associated with the new treatment.

The uncertainty in evidence also makes the countries lean on real-world data. The support from real-world data is seen in the following quote; *"We need to connect the uncertainty to follow-up and to real-world data evidence generation" (Appendix 3.B p. 3, l. 24-25).* All of the countries use this form of data collection in relation to OMPs. However, DK1 is concerned about the adequacy of follow-up in the clinical setting of RDs, which is seen in the following quote; *"(...) problems with orphan drugs are that much of the follow-up data will be on very few patients again, and it will be difficult to conclude anything statistically"* * *(Appendix 3.C p. 5, l. 14-16).* Since the characteristics of RDs are

a small patient population, this solution may run into the same problems with uncertainty, which was the reason that this solution was proposed in the first place.

6.1.3.2 PROPOSED SOLUTIONS

TRANSPARENCY

The most frequently mentioned challenge and strategy is based on lack of transparency; therefore, this was suggested as a solution by the majority of respondents. NO1 suggests transparent R&D costs, as R&D costs are not believed to be reflected in the proposed price *(Appendix 3.A p. 5, l. 11-13)*. This suggestion is primarily expressed in relation to negotiating a fair price for OMPs, because lack of transparency in R&D costs, for example, can cause misjudgment of what a reasonable price is. As one of the influential strategies used by the industry is creating information asymmetry, transparency can eliminate most of the challenges faced by the HTA agencies.

The respondents suggest transparency in regard to current confidential prices as well. DK2 also suggests that transparency, in general, could limit the pharmaceutical companies' freedom of act *(Appendix 3.G p. 10-11, l. 31-1)*. According to the theory of information asymmetry, more transparency can limit the freedom of act for the pharmaceutical companies, as both parties then would have equal information regarding the price. The buyer power also increases as the procurer becomes more informed about the drug. Simultaneously, the occurrence of adverse selection can be limited, and thereby minimizing the economic benefits of the industry.

CONDITIONAL APPROVAL

One of the other prominent challenges faced by the HTA agencies is uncertainty in the evidence. This challenge is suggested by DK2 to be addressed with conditional approval. This solution is conveyed in this quote; *"(...) you will be able to use it like the NICE cancer-drug fund model, where you can just go in and say, during this period we pay this for the drug, until you have proven this, then we can reassess whether there is a greater willingness to pay for the product when we've clarified that uncertainty"* * *(Appendix 3.G p. 5, l. 12-15)*. This set-up can help to constrain the budget spent on these patients. The proposal is an exchange influence tactic, as the buyer promises the seller to reciprocate with consideration of higher WTP if the uncertainty is clarified in a predefined period. Both parties can benefit from this. Although the expenses to provide additional data can be reflected in the proposed price for the drug as an increase. The exchange tactic of considering higher WTP can

backfire, as this makes room for the industry to, subsequently, raise the price of the product and leverage for even higher WTP.

CENTRALIZED APPROACH

After marketing authorization, the EU member states are on their own, assessing each drug's reimbursement decision. DK2 suggests that EMA could work further with the centralized procedure and set some general criteria at the EU level. These are some of the things which DK2 suggests in regard to the centralized procedure; *"(...) a willingness to pay, which is not only national but perhaps European for what the countries wants to give for this type of medicine. Or should you ask for a price range when you approve in the EMA, to avoid these national approval processes which the industry is clearly playing up"* * *(Appendix 3.G p. 10, l. 26-29).* A common WTP provides a benchmark, making it easier for the member states to be aware of a fair price range. DK2 presumes that the industry will not be able to strategize, as currently if the WTP is similar in all countries. A common WTP can, to an extent, eliminate market segments and price discrimination, as every country has similar price limits. Furthermore, transparency will be promoted in relation to the price ranges charged in the individual countries. However, the fact that some countries get large discounts will not last, and all countries will get almost equal prices.

6.1.3.2.1 COLLABORATION AS A SOLUTION

Another solution with a more centralized approach for handling OMP is a Nordic collaboration. The possible outcomes of a Nordic collaboration are discussed, including the criteria for a solid collaboration foundation. Furthermore, the advantages and disadvantages of collaboration are acknowledged by the respondents and described in this section.

ADVANTAGE OF COLLABORATION

BETTER POSITION IN NEGOTIATION

Collaboration is discussed as a solution for reducing the prices of OMPs, as the respondents argue that collaboration will increase negotiation power. The theory is that a larger market is more attractive for the sellers; therefore, sellers will tend to compromise more to get access to that market. The relation between negotiation power and collaboration is seen in SE1 quote; *"I think when you put the Nordic countries together, we become the 12th biggest economy in the world or something like that. So, I mean it should really be a substantial purchasing power buyer influence, if they could unify (...)" (Appendix 3.B p. 7, l. 8-11).* The larger markets give higher access to more patients at once,

allowing buyers the opportunity to request quantity discounts, as the quantity demanded is higher *(Appendix 3.F p. 6, l. 12-13).* This can also be supported by second-degree price discrimination, as lower price follows large quantities. As demand rises for a particular product, the more the unit price can be lowered. The companies use an argument that they need to recoup investment costs from a small patient group; if this is true, access to a larger market should lower the unit price as a ROI is captured from a bigger patient scarce than before. This fact can be used to rationally persuade companies by factually pointing out, that the company will lose access to four countries if not agreeing to the negotiated price. As SE1 points out, the Nordic countries comprise a significant market, determining a high buyer power, and influencing the seller to provide lower prices.

All the respondents agree that collaboration between the four countries could enable a higher negotiation power among procurers than negotiating companies. DK2 reasons that countries not working together can lead to the companies using one country to pressure another country into agreeing to a specific price *(Appendix 3.G p. 7, l. 7-9).* Using the recommendation status in one country to persuade another country is also what is referred to in the strategies used by companies. When collaborating, this strategy posed by the companies can be overcome as there will not be any market segments in the Nordic countries. This eliminates any information asymmetry regarding prices and access conditions, which can be used to influence other countries' reimbursement decisions. The buyer power also increases, as information is shared across borders in the Nordic countries, and the individual HTA agencies become more informed than before collaboration.

HIGHER ACCESS LEVEL

Current high prices restrict the number of patients who can get access to a new drug. For those RD patients without any existing effective treatment, access to new treatment could increase *(Appendix 3.E p. 4, l. 1-3).* Presuming that the prices would be reduced as a result of collaboration, the patients suffering from RDs would have a higher likelihood of getting access to treatment. The opportunity cost of allocating resources to RDs is minimized and makes more room for other disease areas in the healthcare budget.

PHARMACEUTICAL COMPANIES' BENEFITS

Respondents argue that the benefits of collaboration do include not only the HTA agencies but also the pharmaceutical companies. The market segments provide the companies with benefits, as they can price discriminate and obtain maximum prices from each segment. However, when the countries

form a collaboration, it will benefits companies by providing them access to the four countries simultaneously, which is seen in this quote by DK1 *"(...) so I do believe that an international collaboration will be beneficial. Because it is clear that if they know they are getting five times as many patients because they receive the same recommendation in all the Nordic countries, I think they will be willing to, for example, reduce their price"* (Appendix 3.C p. 9, l. 17-19)* which FI2 agrees with *(Appendix 3.E p. 2, l. 28-29).* These are both answers to the questions regarding the improvement of negotiation between procurer and industry. Nonetheless, this benefit is only proven correct if companies value price discrimination less than access to more patients at once.

DISADVANTAGE OF COLLABORATION

DIFFERENT OUTCOME

Even though the respondents point out some of the advantages, they also make it clear that some of the countries could potentially experience adverse outcomes of collaboration. As established before, the respondents assume that larger markets obtain large discounts. Therefore, differences in market size among the Nordic countries can result in bigger countries losing these large discounts. NO2 puts forward this concern in the following quote; *"Sweden they do this assessment, and they have a larger population than Norway, so in theory, I would think they get bigger rebate than Norway, so maybe Norway will benefit from this, but these are all speculation. Theoretically, the smaller countries would benefit if we joint forces" (Appendix 3.F p. 7-8, l. 32-3).* The outcome of collaboration can hypothetically leave bigger countries worse off than prior to collaboration. This theory presented by NO2 is supported by third-degree price discrimination and buyer power. The larger market has higher buyer power, which means they can negotiate lower prices.

DISUNITY

Collaboration denotes that every collaborating parties should agree on how to handle processes. However, sometimes there might be disagreements about certain things. In continuation of the theory that larger markets will be worse off by collaborating, a situation where the countries do not agree on a negotiated price can arise. NO1 mentions,

"But it could be difficult because we could end up with a situation where, this is just hypothetical, that Sweden and Denmark would say yes to the price, but Norway would say no and Finland would say no. As an example, then Sweden and Denmark say okay yes, we will do this, but Norway would say no, then we have a problem, because should we then commit to the no because Norway is not

satisfied? Then Norway goes through another round themselves and gets a lower price, then Sweden and Denmark would feel shit we could have a better price" (Appendix 3.A p. 6-7, l. 26-1).
If not all parties in the collaboration are satisfied with the agreement achieved, this can lead to separate negotiations. The disagreement upon various aspects can make the collaboration inefficient and impractical. If the collaborating countries do not reach an agreement, there will be no point in collaborating, as the outcome will be the same as if they negotiated separately.

CONTROLLED BY THE COMPANIES

Collaboration is described by the respondents as a solution to handle the challenges resulting from OMPs. In this relation DK1 points out the following; *"Right now, there are joint assessments, being made in Norway and Sweden, which are also managed by the companies. The companies first indicate that they want a joint assessment and they have to sign that's what they want, and things like that. Then they have a free choice they can go into one process or the other" * (Appendix 3.C p. 11, l. 18-21).* In continuation hereof, DK1 mentions that if the collaboration process is optional and the companies have to choose, then joining forces might not work, as the companies can estimate which process will give them the most beneficial outcome and choose that one. The disadvantage of doing so is to give companies yet another way to strategize. As companies have the choice between two processes, the power is no more by the procurer, but the companies.

ATTITUDE TOWARD COLLABORATION

Based on the advantages and disadvantages presented by the respondents, the general attitude toward collaboration is positive among respondents. Mainly, the respondents agree that an increment in buyer's power will follow collaboration. However, not all countries agree that the outcome will be beneficial for everyone. Nonetheless, the disadvantages may outweigh the advantages if an unassailable collaboration foundation is not established aligning the needs of all parties. Furthermore, several barriers are yet to overcome to make this a reality.

BARRIERS TO OVERCOME

DISCREPANCY AMONG COUNTRIES

Certain aspects might differ between the countries, which is considered an obstacle for collaboration. A factor that is important for the countries to agree upon is the WTP. If the countries do not have the same WTP, then the disadvantage of *'Disunity'*, mentioned above, can be a reality. Currently, there

are different WTPs in each country; Norway has a WTP of NOK 275,000 per QALY for non-orphan drugs, whereas the WTP is 500,000 for Sweden and can be elevated up to SEK one million *(Appendix 3.A, p. 3, l. 2-3 and Appendix 3.B p. 2, l. 26-27).* The necessity of an agreed WTP is a common understanding among the respondents.

The valuation of new data goes hand in hand with the common WTP, which is mentioned by SE1, *"We have these additional data are we going to double the price, half the price or half the patient group, so that the consequences of the different range of new data inputs are made clear (...)" (Appendix 3.B p. 3, l. 25-27).* It is not enough to agree upon a basic WTP, but also making evident what value less uncertainty in data brings.

DK2 is, on the other hand, concerned about the various timings in each country: *"(...) first of all, we have three different approval processes, so it has to be timed so that the processes of each country fit" *(Appendix 3.G p. 8, l. 4-5).* Denmark has a 12-week assessment process, restricting them to a particular timeframe, however, this is not mentioned by the other respondents, making it important to compromise on a timeframe suiting all countries. Along with timing, the method of assessment should also be consistent. According to DK1, it will be difficult to propound a negotiation proposal if all countries have different assessments *(Appendix 3.C p. 10, l. 26-27).* Compared to the other Nordic countries, Denmark has a different approach to evaluate new drugs, as mentioned previously.

POLITICAL SUPPORT

The degree of governmental influence is explained by the respondents in various relations, for example, as a challenge and a strategy used by companies. Therefore, the political support from each country is essential to obtain efficient collaboration between the countries. DK1 expresses the need for political support in this quote; *"So I really believe in an international collaboration. But I only believe in it, if there is also a political will for us to comply with each other. We need to know from the politicians, well you can wait for Norway and Sweden to be ready, and it may take six months (...)" * (Appendix 3.C p. 10, l. 19-22).* The support should not only be according to the processes themselves but also a will to consider all patients apart from those in the respective countries should be present. FI1 doubt that national authorities are ready for supporting collaboration *(Appendix 3.D p. 6, l. 17-19).* FI1 uses the argument that national authorities want to prioritize their patients before worrying about foreign patients.

NON-COOPERATIVE COMPANIES

In the disadvantages, it is mentioned that the pharmaceutical companies have a say in what process they wish to go through, in existing collaborations. Companies are important stakeholders, which means they have to cooperate in order for collaboration between HTA agencies to work. In this relation DK2 explains, *"The intention agreement signed by the Ministry, says we can make joint negotiations and we tried it once, but we didn't get through with it, because the industry didn't want to be part of it"* * *(Appendix 3.G p. 7, l. 21-23).* The barriers to overcome when initiating a collaboration are coming from both HTA agencies and pharmaceutical companies. As DK2 describes, a collaboration between the HTA agencies must be supported by the companies to work properly. DK1 agrees with DK2 and argues that the companies obtain better profit by price discriminating than negotiating with several countries at once *(Appendix 3.C p. 11, l. 11-14).*

6.2 PRELIMINARY GUIDELINE FOR EFFICIENT CROSS-BORDER COLLABORATION

This section outlines a preliminary guideline based on the respondents' statements to plan a cross-border collaboration in the Nordic countries. Primarily, this guideline builds upon the *'barriers to overcome'*, as these should be addressed and solutions for these identified before entering a collaboration. In the following guideline, the tasks discussed in the interviews are marked with a green tick, whereas those marked with orange ticks need further consideration.

	Task	
WHO	*Collaborating partners*	
	The Nordic countries (Denmark, Finland, Norway, and Sweden)	✓
	Establish an agreement for working together (including the terms of participation and commitments)	
	Common purpose	
	Better prices for OMPs	✓
	Identify other desired outcomes	
	Collaborative process	
	Four separate national assessment processes with a joint assessment of individual outcomes to jointly negotiate and procure OMPs	✓
	Key roles and relationships	
	Establish each country's role and responsibilities in the collaboration to maximize the beneficial outcome of working with the challenges	✓
	Identify resources and capabilities of each organization	
WHY	*Expected outcomes*	
	Positive expected outcomes of cross-border collaboration include *better position in negotiations*, *rebates,* and *higher access (see advantage of collaboration)*	✓

	Negative expected outcomes of cross-border collaboration include *different outcomes* and *disunity (see disadvantages of collaboration)*	✓
	Determine other expected outcomes subsequent to establishing fundamental processes of collaboration, that is the four prior tasks	
	Work further to identify possible future challenges with collaboration	
	Concern of *disunity* should be addressed by an agreement prior to collaboration to avoid this outcome, and avoid that any country is worse off by joining the collaboration	
	Information gathering of challenge	
	The challenges with OMPs are similar across the four countries *(see challenges faced by HTA agencies regarding OMPs)*	✓
	Confirm every partners' understanding of the information about the challenges and that these are actually considered challenging for everyone	
	Current environment	
	The main external factor influencing each country is the economic one, as most of the challenges emerge from this factor when assessing OMPs at a national level	✓
	Look at the PEST analysis and identify which external factors are considered the most significant challenge and prioritize resources to deal with this	
WHAT	*Effective national processes*	
	Effective national processes are identified as Denmark's categorization of added value *(see proposed solutions)*	✓
	Use a process map to outline the current national processes for each country and identify the effective processes are in each national system	
	Define the strategies used by the industry and add those in the process map, where they affect the processes (This makes it possible for the partners to identify ways to cope with these strategies in collaboration)	✓
	The proposed and current solutions, should be discussed and evaluated further, in regard to their applicability in collaboration for achieving the desired outcomes	
	Co-creation and not able to do alone	
	Better position in negotiation, is found to be an aspect which cannot be achieved by the countries if they work individually *(see advantages of collaboration)*	✓
	The strategies price confidentiality is easier to confront when the countries collaborate as there is no room for information asymmetry between the countries	✓
	Identify what a collaboration is able to provide each country which is impossible when working separately	
HOW	*Aligned work plan*	
	Identify differences in national processes, which could be barriers for collaboration Most of the respondents mention that a barrier to collaboration is a timing, method, and political support *(see barriers to overcome)*	✓

	Harmonize/align these processes In regard to method, Denmark is going to use QALY, which is a step toward alignment	
	The collaborative structure	
	Based on this thesis, the collaboration is going to be a joint negotiation and procurement	✓
	Partners should discuss other options according to the outcomes they desire to obtain, apart from those covered in this thesis	
	It should be discussed which structure is most suitable for the partners; one team in charge, smaller teams or individual work until joint negotiation	
	Measuring success and progress	
	Complete one collaborative case and evaluate progress, success and faults which should be improved Measures of success: - Compare prices prior and after collaboration - Compare timing from application to access - Compare workload of each HTA agency	
	Identify subsidiary aims to measure progress Example; - Timing during assessment - Workflow	

7 DISCUSSION

7.1 MAIN FINDINGS

This thesis has shown that the HTA agencies in Denmark, Finland, Norway, and Sweden are facing various impediments when assessing OMPs, from methodological to economic sustainability. It is profoundly agreed upon that the most commonly occurring challenges are vast uncertainty in evidence as well as high prices proposed by the companies. However, the four countries have addressed these with various solutions, suiting their national methodological approach. Drugs are primarily measured and valued according to additional criteria. One of the common suggestions to overcome the high prices has been transparency, as it eliminates information asymmetry. As collaboration can promote transparency among the collaborating countries, the majority of respondents have a positive attitude toward collaboration. Cross-border collaboration can contribute to higher purchasing and bargaining power to the countries due to the formation of a larger market. However, thorough planning is a necessary means of obtaining efficient collaboration. The preliminary guideline presented in this thesis needs to consider all relevant perspectives, both internal and external, to increase its validity and credibility.

7.2 FINDINGS FROM OTHER STUDIES

The various challenges, such as high price and evidence with great uncertainty identified in this thesis, were, to an extent, common apprehension among the respondents. A study by Nestler-Parr et al. (39) also found the uncertainty in evidence to affect the decision-making of OMPs, as it was negatively correlated to the OMPs reimbursed price and status. Generally, the HTA agencies use cost-effectiveness analyses, requiring robust evidence to evaluate drugs. However, this evidence is difficult to collect for RDs, which is why the respondents expressed that they use alternative evidence and apply other criteria to minimize uncertainty. When WTP is estimated, it is typically based on the incremental cost-effectiveness ratio, which is often exceeded due to the high price, and the treatment is not recommended. This arises a conflict between value for money and ethics, as a risk of not providing the patients with access to the right medicine arises.

An article by Morgan et al. (40) argues that price confidentiality serves the industry best, as it is a strategy to avoid all countries demanding the lowest price available. The companies can get access to more countries than if the prices were transparent. Market segmentation is a way for the industry to keep the countries apart and strategically obtain the maximum price for the drug as possible.

Furthermore, the presence of confidential prices results in procurers paying the maximum amount without knowledge about the possibility of lower prices, thereby inefficiently displacing higher values for patients. Additionally, the companies set the initial prices high, which is substantiated with the argument of ROI from R&D. With the uncharted R&D costs, information asymmetry arises as the procurers are unaware of the investments made by the company. Morgan et al. (40) identified the costs of the drug Ivacaftor for a subtype of cystic fibrosis, which was $300,000 per patient per year in the United States. The manufacturer of Ivacaftor earned a global net revenue of $3.65 billion in the period from 2014 to 2018, with an additional $4.68 billion for combination medicine over the same period. This suggests that the R&D costs might not be as high as the companies argue. Furthermore, the clinical trials are small, which is presumed to incur lower costs with gathering evidence, however, it is not evident that all manufacturers have low R&D costs associated with OMPs. According to a review by Simoens (41), some manufacturers have to recoup expensive R&D costs from a small group of patients, whereas other drugs are approved based on historical use. The latter has no associated R&D costs, as the production of new evidence of efficacy is not required to gain marketing authorization.

EMA implemented the orphan designation to incentivize the development of OMPs, but over the years, this has been used as a strategy by companies to profit. Simoens (41) reports that companies use salami-slicing strategy by dividing diseases into smaller subcategories to gain orphan designation for each subcategory. The orphan designation resulting in higher prices is, for instance, seen with Revatio, a drug for pulmonary arterial hypertension that became six times more expensive after obtaining an orphan indication for another disease. The manufacturers can receive multiple indications, even orphan indications, for the same drug. In the case of Imatinib, a drug approved for six orphan indications in the EU, the manufacturer can profit from monopoly pricing in all six indications. (41) The manufacturer can take advantage of this by applying for one indication and gradually applying for others as the profit minimizes. Hence, it is debatable whether the systems and regulations make room for the industry to strategize. Companies justify these high prices with RDs' debilitation of health and the necessity to improve patients' well-being. The negotiation power of the HTA agencies is limited, and the political pressure of providing treatment for RD patients significant. These factors combined create a market where there is an increased price inelasticity allowing the manufacturers to charge the highest price that market will allow, without any change in demand.

In order to address the challenges regarding the high prices of OMPs, transparency is suggested as an effective solution in this thesis. Vogler et al. (42) agree that transparency might reduce prices, as most

countries use external reference pricing. However, it is difficult to say whether this will lower prices for every country or if it will result in higher prices for those countries obtaining a lower price with the confidential pricing. According to Roos et al. (43), companies avoid downward price referencing between countries; if transparency is implemented, the risk of even higher prices arise. With confidential pricing, countries are unaware of each other's confidential discount prices and cannot use these as references. Transparency provides price information, which in return allows procurers to ask for lower prices than the countries which already reimbursed the drug. To avoid lower profit, companies will seek new strategies and increase the prices to profit the same as with confidential pricing. Vogler et al. (42) agree that in the presence of transparency and widespread use of external reference pricing, manufacturers are incentivized to launch in countries with higher drug prices to avoid lowering the average price levels. This incentive can lead to neglected or delayed access in other countries.

Another aspect of this is, if the procurers expect transparency, the industry might expect the same from procurers, resulting in other controversies, as the procurer needs to be more transparent with, for instance, their method of assessment and WTP. Bertram et al. (44) suggest that the industry can use transparency in WTP as a tactic to tailor their offers based on the publicly available threshold. The procurer will, in return, have a difficulty saying no to drugs, with an ICER within this threshold. Since a WTP does not provide information about the affordability of implementation, this can cause an increase in spending. In the instance of Sofosbuvir for hepatitis C patients, the United States operated with a threshold of $100,000, which required a 4 % national increase in pharmaceutical spending for these patients. Thus, it is immensely important to consider the practical outcomes of the solutions before implementing them because they may turn out to be adverse as well as beneficial.

In this thesis, collaboration is suggested as a solution to enhance the procurers' position in negotiation when facing increasing prices of OMPs. Vogler et al. (42) agree with the respondents that a collaboration could be a way of partially overcoming information asymmetry and the lack of transparency while enhancing purchasing power. Some procurers can be opponents to this, as they might be by the conviction that they are currently getting the best price discounts.

At the same time, the respondents state that pharmaceutical companies will also benefit from collaboration among procurers. However, Vogler et al. (42) point out that the industry will most likely be adversaries of this because they might attach more value to information asymmetry. Companies can benefit from getting access to more patients simultaneously, but the companies should, in return, be willing to give up price discrimination. This expense is rather unlikely as price discrimination results

in higher profits for companies. The existence of confidential prices and agreements between the procurers and industry makes it difficult to assess which solution would be most beneficial for both parties. Therefore, companies' perspective would permit an insight into what the industry value most; the process as it is now, or the hypothetical outcomes of collaboration. Eatwell et al. (45) have studied the industry's perspective, and a representative of the industry, exhibit a positive attitude toward collaboration if the assessment processes are quicker, in all collaborating countries, without any delays. *'Barriers to overcome'* are important obstacles to take into account before collaborating. The respondents recognize the need for the collaborating countries to have similar methods in their national processes to obtain an efficient collaboration. Seng Lee et al. (46) agree with this, as countries with similar healthcare systems tend to achieve better collaboration. In Denmark, Finland, Norway, and Sweden, there are several similarities between the countries' healthcare systems, but Denmark differs in its methodology of the assessment process. The Danish HTA agency is working toward a QALY model, making it easier for the four countries to collaborate. However, a WTP is not implemented, according to L.P. Vestergaard, a member of the Danish Medicine Council (47). A common WTP was one of the factors which should be aligned in collaboration, but this might not be as easy as it seems. Even if the Nordic countries present similarities in healthcare, a disagreement can emerge considering the value of a health benefit especially in monetary terms. A common WTP should reflect this value and the opportunity cost which each country allocates. The heterogeneous nature of RDs present a difference in disease burden for each country, which follows various values attached to these diseases. Even if an agreement is reached upon a WTP, some of the countries might end up with a higher opportunity cost than the others. Furthermore, as seen in *'Discrepancies among countries',* there is a significant difference between the thresholds with which Norway and Sweden operate. These thresholds represent the value which the countries attach an increase in QALY, and it is questionable whether Norway is willing to increase, or Sweden decrease this threshold. Several consequences of obtaining a common WTP are present and should be addressed first; maybe a WTP range could be considered instead.

Another obstacle worthy considering is the political pressure on timing in Denmark. When aligning the countries' processes, both political support and timing are considered to be important fundamentals to align. The political pressure in Denmark can have consequences for the other countries when collaborating. The issue is that DK1 believes, their high prices are due to Denmark being one of the first countries to recommend a drug. The other respondents did not mention any timewise pressure,

which means that the Danish 12-week assessment can dominate collaboration timing. Consequently, the collaboration can lead to higher prices for all four countries, according to the statement of DK1. The preliminary guideline proposed by this thesis is based on the respondents' answers in the interviews, but further research has to be conducted before establishing a definite collaborative model. Seng Lee et al. (46) suggest different approaches for collaboration within the ASEAN structure, which could be the road ahead when structuring a cross-border collaboration among the Nordic countries. One of the important approaches presented by Seng Lee et al. (46) is to formulate a legal framework as the difference in the political setting in each country can be a barrier for collaboration, which is also a concern expressed by the respondents. Hence, a harmonization procedure with a focus on different elements in the processes has to be deliberated to obtain effective collaboration. This thesis does not take into account harmonization, and therefore the preliminary guideline only serves as a compilation of different aspects to consider before establishing a collaboration framework.

7.3 Strengths and limitations

As this thesis progressed, some limitations were encountered, among these the chosen perspective. The only perspective considered in this thesis is the procurers', which merely contribute with inputs from the HTA agencies and leaves other stakeholders out. The industry is a crucial player in the assessment process, and consequently, it would have been beneficial to incorporate them to get a broader comprehension of the context. Inclusion of the industry's perspective would have been helpful to gain insights into reasons for collaborations as well as the disadvantages of collaborations for the industry. Further, this would enable an understanding of the industry's requirements for partaking in collaboration. Including the industry perspective, could have permitted a comprehension of how the industry and the procurer interact and react to the opposite party's actions. Other valuable perspectives comprise those of other stakeholders, such as policymakers. The policymakers' perspective would give access to the requirements for the political and legal framework of future Nordic collaboration, including necessary political actions before collaboration. Ideally, all stakeholder perspectives should have been included to prepare a guideline for collaboration that suits all stakeholders' needs and values, minimizing the risk of a failed collaboration.

Apart from the perspective of this thesis, the number of respondents may limit the research horizon. This thesis is based on seven respondents' assertions; thus, too few respondents for the results in this thesis to be generalizable. The outcomes of this thesis are less reliable, as the number of respondents is not sufficient to represent four different HTA agencies. However, all four countries of interest are

represented, illustrating the attitude toward collaboration from each of these HTA agencies' standpoint. This thesis can be used for basic knowledge of how the attitudes toward collaboration may be in each of these Nordic countries. However, it is not sufficient to say whether most of the procurers think collaboration is the way to cope with the challenges of OMPs. Even though the interviews' perspective does not include all stakeholders, more respondents would at least have given greater insight into the general attitude and outcomes of collaboration.

A question of generalizability of these challenges arises, as the categorized challenges result from one-on-one interviews. Since the respondents were interviewed alone, only an individualistic view is disclosed. Alternatively, focus group interviews could have contributed to a broader range of information based on the interaction and discussion between the respondents. By adopting focus group interviews, the internal challenges, and also the internal relationships, in each organization might have been emphasized. On the other hand, using focus group interviews could have suppressed information that some respondents might hold due to colleagues' presence. The respondents can tend to share what is considered more ethically and politically correct to avoid treading on other's toes. The topic of this thesis involves a great amount of confidentiality, politics, and relation with the industry, which is why it can be a sensitive topic to discuss in a broader group of people. Focus group interviews could have brought more bias into the results when discussing the challenges and solutions of working with OMPs. Accordingly, a combination of individual interviews and focus group interviews would have been the optimal solution for gaining more insight into the more generally affecting challenges and recognizing the bias in the interviews.

The challenges put forward by the respondents in this thesis were analyzed according to PEST analysis, to analyze the external factors affecting the organizations. However, the resulting use of this analysis can be limited, as the external factors identified based on the statements are not critically examined to what extent they impact the organizations. In that optic, it is difficult to measure what value this analysis has to the later strategic planning and prioritization of resources to address the individual external factors when aiming for collaboration. Furthermore, the categorizations of these challenges are based on interpretations and assumptions of what the respondents expressed in the interviews and not a proper market analysis to put the results in perspective. Insufficiency is also evident in the fact that this analysis does not consider internal factors within an organization, which can also be the cause of the challenges. Nonetheless, to strategically plan an efficient collaboration between the Nordic countries, this tool is convenient as a step toward a market analysis.

7.4 IMPLICATION OF THIS THESIS

This thesis is important, because it provides a basic understanding of how the representants from the Nordic countries respond to the idea of a Nordic collaboration, and the measures they believe are important to take, in order to obtain an efficient collaboration. The consideration of a collaboration between Nordic countries are of great importance, as these countries encounter similar challenges regarding OMPs and a collaborative approach can potentially strengthen the effort to overcome these. Currently, several collaborative arrangements are present in the Nordics countries as well as in the EU, for which reason it is important to understand why these have not been harmonized into one collaboration among the countries. Furthermore, the Nordic joint negotiation on Zynteglo, a gene therapy taking place in June, contributes to a renewed topicality of this thesis, as FINOSE and Denmark are to complete two separate assessment processes before jointly negotiating. (48) This thesis is a step toward the understanding of the mechanisms behind a common approach for countries to oppose high OMP prices. By including more countries in further and similar research, exhaustive knowledge about harmonizing the collaborations in the EU can be obtained. A focus on the OMP market is important as current incentives to promote the development of OMPs have led to the formation of a business market in which companies, by and large, have the power. (49) This has resulted in vastly high prices without any effective solution to manage the uneven power-relation between companies and procurers. This thesis highlights the importance of a solution that distributes equal power to procurers in a negotiation without any detrimental effects for other stakeholders. Collaboration might contribute as a compromising solution to maintain the industry's interest in this niche market and at the same time pay regard to the procurer's economic affordability.

8 CONCLUSION

In conclusion, OMPs cause various complications across the Nordic countries for both HTA agencies and other stakeholders. These are dealt with differently by each Nordic HTA agency. Mostly these challenges lead to affordability issues and concerns regarding value for money. The consensus on challenges regarding OMPs indicates that it might not be a country-specific issue and forms the basis of the necessity for a collaborative approach. However, there is a considerable number of barriers to overcome in order to obtain an efficient collaboration with the HTA agencies' desired outcomes. These barriers are taken into account in the preliminary guideline. Nevertheless, to establish a more valid guideline, it is important to incorporate all relevant perspectives, both internal and external, to make a more evidence-based decision. The barriers identified are predominantly a consequence of the concern about the lack of cooperation from other stakeholders. If all stakeholders are willing to cooperate, it is possible to obtain an effective collaboration and gradually extent the number of participating countries. Further research is needed to establish the willingness of other stakeholders to cooperate in a potential collaboration, so no one is worse off with this solution. A prospective research is required to definitively conclude, whether a cross-border collaboration between the Nordic countries, can be applied in practice and whether the resources invested in the organization hereof are equally worth for all stakeholders.

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