Rare disease thresholds

-An analysis of different definitions, laws and arguments

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ABSTRACT

Background: The aim of the thesis was to investigate what the thresholds for what constitutes a rare disease around the world are, what are the arguments for them, how they have evolved and what are the implications. The thresholds may have increasing implications for both legal framework and health care budgets. The health care budgets may be affected to a higher degree than before since, we are in the era of specialized medicine and the drugs now offered comes at a high cost. There is normative discussion about the ethical obligation to treat everyone regardless of the cost and whether the laws on orphan drugs is the most effective means to make pharmaceutical companies invest in new products for rare diseases.

Methods: The thesis is a semi systematic literature review conducted using a "snowballing" technique. The data presented are qualitative.

Results: The thresholds differ greatly around the world, but they are converging. This is especially true for the countries with the highest GDP. Although not defined in official documents, the ethical arguments to consider rarity as a criterion when reimbursing orphan drugs appear to be the same around the world. There are several examples on how the pharma sector are adjusting their strategies to comply with the legal framework.

Conclusion: The variations in the threshold for when a disease is considered "rare", and the disagreements about the normative arguments for giving weight to rare diseases, combined with strategies and technologies that split diseases into smaller groups, indicate a need to rethink the current laws.

ABBREVIATIONS

CAGR: compound annual growth rate

CEA: cost effectiveness analysis

CORD; Canadian organization for rare diseases

DMD: Duchene Muscular Dystrophy

DRC: The Drug Reimbursement Committee

EMA: European medical agency

EU: European Union

FDA: Food and Drug Administration

GDP: gross domestic product

GNI: gross national income

ICER: incremental cost effectiveness ratio

ICORD: International Conference of Rare Disorders

INSERM: French National Institute for Health and Medical Research

IRDiRC: The International Rare Diseases Research Consortium

HTA: health technology assessment

MHLW: Japans ministry of health, labor and welfare

MRDS: Malaysian rare disease society

NHS: national health system

NKSD: Nasjonal kompetansetjeneste for sjeldne diagnoser

NORD: National Organization for Rare Disorders

NSCLC: non-small cell lung cancer

ODA: Orphan drug act

ODTC The Orphan Drug Tax Credit

PPP: purchasing power parity

QALY: Quality Adjusted Life Years

QoL; Quality of Life

R&D: Research and development

RCT: randomized controlled trial

ROI: return on investment

RR: rule of rescue

SMA: Spinal muscular atrophy

WBG: World Bank Group

WHO: World Health Organization

WTP: Willingness to Pay

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1.0 INTRODUCTION

One of our most important medical innovations in recent years are our ability to identify rare diseases with the use of genotypes (Listgarten, Stegle, Morris, Brenner, & Parts, 2014). Because of the innovation provided, what we consider to be a rare disease also changes and the number of identified diseases increases manifold. Many countries have defined thresholds for what constitutes a rare disease and have laws that regulate the approval of pharmaceuticals for these conditions.

In this thesis, I will investigate the different thresholds and the ethical argumentation on whether we should consider rarity when considering reimbursement. I will investigate the legal system put in place to protect the patients, and the incentives offered to the pharmaceutical sector to produce the orphan drugs society needs. Lastly, I will look at how the pharmaceutical sectors adapts to the legal framework, and the normative arguments on what the public values when deciding on reimbursement.

My personal interest for this topic came as a result of the drug Spinraza, for the rare disease Spinal Muscular Atrophy (SMA) being denied for reimbursement in Norway for patients above 18 years. This decision was made on the basis that there was not enough evidence for effect for adults. This denial of reimbursement led to public outcry, and the patient organization for SMA sued the Norwegian government. The lawsuit has recently been dropped, but the ethics around the decision and the question if we should value rarity was, and still is heavily discussed.

My research question is therefore: *what* are the different thresholds for a rare disease around the world, *how* does one argue for the different thresholds and rarity, and *what* consequences may the thresholds lead to.

The thesis consists of several chapters, with chapter one being the introduction. In chapter two; I describe my theoretical framework. In this chapter I present what the previous research has discovered on the subject, but also what it lacks.

In chapter three I describe how I conducted my own research and which methods I used.

In chapter four, I will present the results from my research and lastly in chapter five, I will both discuss and conclude on my findings.

2.0 THEORETICAL FRAMEWORK

There literature surveyed indicated that there is little theoretical research on the precise definition of when a disease is to be considered rare. There is, however, a relevant theoretical literature on the ethical arguments about priority setting. Specifically, there is a theoretical literature that deals with whether rarity should be considered in the priority setting process and when evaluating the costs and benefits of a drug. The previous research did not however combine the research on thresholds with the ethics, normative arguments and implications that the thresholds provided could lead to.

My contribution to this reasearch is that I have made a summation of several countries, and included the arguments /motivation for the threshold, but also what incentives the different countries offer to produce orphan drugs. I will not try to define what the thresholds should be in this thesis, but rather find how the thresholds have evolved, and how the pharma industry adjusts to the legal implications of the thresholds.

How the threshold is defined is vital since the definition, and hence the rarity concept is often used when deciding on reimbursement and incentives provided for the pharmaceutical sector. With the expanding number of rare disorders, it also becomes interesting to look at how one argues for it to be rare. This is important to understand because with the increased use of personalized medicine; we would in the end, be stuck with an endless group of "rare" patients in health care (Juth, 2017). The literature has shown that there is not a consensus on what is considered a rare disease either.

2.1 What is a rare disease

My research has shown that there is not a single definition of what a rare disease is and Richter and colleagues (Richter et al., 2015) found in their research that as many as 296 different definitions exist. A disease is defined by OrphaNet (2019) as a change in health state, with different symptoms and one way of treatment. Here, I will think of rare diseases as a collective term used to describe diseases that affect few people compared to the general population. This is a broad way of thinking about the term, and based on this, there is considered that there are between six and seven thousand diseases that can be classified as rare (Orphanet, 2019). It is further estimated that this number will rise by approximately 30

new diseases each year (Aitken & Kleinrock, 2017). Worldwide, it is estimated that rare diseases combined affect approximately 400 million people (WHO, 2013).

The terms rare diseases and orphan diseases are often used interchangeably, and the word "orphan" refers to the fact that these diseases have historically been neglected, or "orphaned", by the pharmaceutical industry (Franco, 2013). We say that they orphaned by the industry since, without incentives, the industry is not interested in developing medicines for such a small number of patients.

Orphan diseases have a wide range of heterogeneity but are often chronic, severe and progressive but not necessarily lethal. 80% of rare diseases have identified genetic origins while others are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative (Sharma, Jacob, Tandon, & Kumar, 2010). 50% of rare diseases affect children, 30% of which will die before reaching five years old (EURODIS, 2019).

Rare diseases also have in common that there is often no or limited choice of therapeutic options (Medic et al., 2017). For most orphan diseases, there is not a cure, but both quality and length of life may be increased with treatment (OrphaNet, 2019). It is however estimated that only 5 % of rare diseases as of 2018 have an appropriate treatment method (Aitken & Kleinrock, 2017; LMI, 2018). Austin et al. (2018) believe this number could be increased to 9 % in 2027, assuming a constant delivery of orphan medical products from the pipelines of the biopharmaceutical industry. This constant delivery is a big assumption since we know the approval rate is decreasing for orphan drugs. What constitutes a rare disease also differs between countries, as one might be common in one part of the world and rare in another. Disease prevalence is further often assumed to be overestimated since studies use data extrapolated from regions of higher prevalence (Tambuyzer, 2010).

2.2 Economics of scale

This definition of rarity and the thresholds becomes an increasingly important economic question as well, as the medical innovation we are experiencing comes at a large cost, with newer specialized drugs offered with high prices, and orphan drugs differ from other drugs in several ways. The standard way of defining orphan drugs, is drugs that are offered for the patient groups that are considered rare, and or drugs that would not been produced without

added incentives (Aronson, 2006). Orphan drugs typically have high prices and hence not considered to be cost effective. This is because the high cost of marketing, research and development, and that there is only a small patient group to cover these costs. Simoens (2011) states that we can also blame the lack of other alternative treatments and limited negotiation power from third party payers for the high prices of orphan drugs. Regardless of why the prices are so high, Kanavos and Nicod (2012) argue that it is important that we let the pharma industry operate with them. They believe that otherwise it is unlikely that the R&D investment will continue and that the current unmet need for rare diseases will remain so in the future.

It is estimated that the development cost for a single successful biotech drug is about $1.2 billion over approximately eight years of testing and regulatory review (Barak & Shankar Nandi, 2011). However, audits in the Genzyme Corporation's accounts suggest that the costs of developing orphan drugs are lower than those of other drugs, since fewer patients are enrolled in the clinical trials (Drummond., et al 2007).The median cost per patient and per year is nevertheless 19 times higher for an orphan drug than for a non-orphan drug (EvaluatePharma, 2014). Our health care budgets are not able to follow in the same pace as these costs, and we are then in a position without access to innovative medications due to economic constraints, and orphan drugs are not considered cost-effective.

They are not considered to be cost effective regarding each quality adjusted life year (QALY) they provide with the cost of providing them. QALYs are a measurement to show the value of one year in perfect health. It captures both reduced mortality and reduced morbidity. QALYs are the product of the years lived (t) weighted by the quality in which that time is lived (q). This is presented in equation 1 below.

$$\mathrm{QALY} = q \cdot t$$

Equation 1: calculation of QALYs

Both two years in a health state of 0,5 (based on EQ-5D), or one year with a score of 1 will provide one QALY (Drummond, Schulper, Claxton, Stoddart, & Torrance, 2015). The Q in the equation is based on the numbers provided by the EQ-5D.

The EQ-5D is a generic measurement to show how one values different health states. In the EQ-5D people fills out on their own health in five dimensions (mobility, personal hygiene,

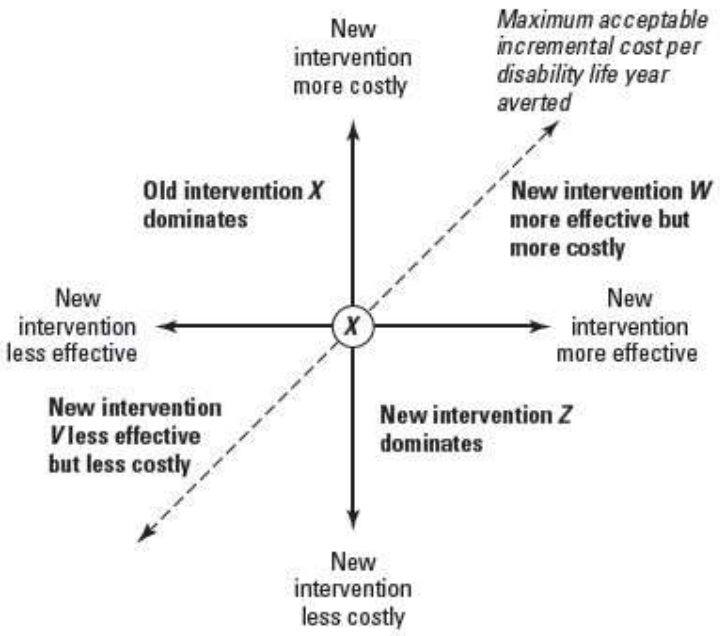
usual activities, pain/discomfort, and anxiety/depression) with three possible responses for each item (no problem, some problem, unable/large problem). This generic measurement developed by EuroQol is useful for several conditions and it is not time consuming to fill out (Glick , Doshi , Sonnad, & Polsky, 2015). The EQ-5d offers values between 0 and 1, with 1 being no problems regarding the question asked e.g. perfect health in that dimension. The results of the EQ-5D are multiplied with time to calculate QALYs. An assumption for QALYs is that they are distributive neutral i.e. a QALY is a QALY regardless of diagnosis it is calculated on (Nord, 1999). A second assumption on QALYs is that they are independent from the previous or following health states (Soares, 2012).

When we have calculated the QALYs, we further decide on what we consider cost effecting by a health technology assessment (HTA). When conducting an HTA, a cost effectiveness analysis used (CEA) is often used. A CEA compares the existing treatments with the new technology. The result of the CEA is then reported as the incremental cost-effectiveness ratio (ICER). An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect). This shows us the extra cost per extra unit, in our case a QALY.

$$ICER = \frac{Costs_{New} - Costs_{Old}}{Effects_{New} - Effects_{Old}}$$

Equation 2: showing how the ICER is calculated

The ICER obtained from the calculation is a point estimate and is further analyzed in a cost-effectiveness plane shown in figure 5 below.



Figur 1: Cost-effectiveness plane.

Source: Drummond (2005) Note that even the model shows DALYs, the plane could easily have been shown with QALYs.

We make the plane by adding the incremental effect on the horizontal axes, and the incremental costs on the vertical axis. The plane now displays four quadrants, and they tell us how costly/ effective the treatment is (Drummond et al. ,2015). An ICER in the south east quadrant is always the preferred, since this means that the new treatment is both more effective and cheaper than the comparator. Observations in the north east quadrant indicates that the new treatment is more effective but costlier. In the case of orphan drugs, we often find ourselves in this quadrant.

2.3 Ethical considerations

The unpreferable results from the cost-effectives analysis provided in case of orphan drugs lead to the ethical question on how society allocates its funds, and how we should prioritize as resources are scarce. It is an interesting ethical question since many scholars believe that QALYs should not be used at all when the only alternative is treatment vs. no treatment. Hyry et al. (2014) states that one cannot calculate ICERs with orphan drugs as there is not an

alternative to compare to and this means that the usual HTA would not give accurate answers in the case of rare diseases.

These arguments from scholars lead to the unanswered question if is fair that people are judged and treated only in terms of how cost-effective their health gain is. This is a difficult question where the literature does not provide clear ethical guidelines. On this a member of the Belgian Drug Reimbursement Committee (DRC) said *"We had a discussion in the DRC once, in which we said, this [decision about the reimbursement of an enzyme replacement therapy for children] is in fact an ethical discussion, and we are not an ethical committee* (Picavet, Cassiman, & Simoens, 2014). As previously described, Health technology assessments (HTA) assumes that we can value someone's utility and suffering adequately, but can we really? Several scholars claim we can, as the utilities in our case the QALYs are calculated by the EQ-5D that again are based on societal judgement. Hence, other things should be considered when deciding on reimbursement. If we contemplate these questions, should we consider the patients rarity as a vulnerability-and hence strive to treat these patients?

It is an ethical dilemma how we should approach the question of how to spend our healthcare funds. People are divided in what they consider important when evaluating ethics regarding decision-making. Although we cannot insure against the risk of getting a rare disease, many people belong to a form of health insurance system, either through the NHS or a private provider to protect against any economic loss a disease may lead to. Should this insurance be any different if the disease is rare? Or should we also here consider that affected patients were just unlucky, and hence society should compensate them for their unfortunate health status? This would be in line with the notion of equal opportunity for health. Others again argue that society considers the total number of QALYs obtained as the most important. There are several schools of thought on this.

The Deontological view of ethics is an individual focused approach; outcomes/consequences may not just justify the means to achieve, but we should only look at if it is the right thing to do for those patients in question[1]. When we look at ethics in this way, we can say that the deontology view is patient-centered (Mandal, Ponnambath, & Parija, 2016).

[1] The term is Greek, and comes from deon = obligation

Garbutt and Davies (2011) describe that with this view, the individual patient should be in focus, regardless of how it will affect the overall budget. With this perspective, we should not consider rarity as a criterion per se, but offer help based on that everyone is to receive the appropriate treatment and hence disregard how it may affect the rest of society. The Norwegian professor, Terje Rootwelt highlights that in our legal framework, we are obligated to offer everyone the best available treatment (Bordvik, 2013). This right is also found in article 12 of the International Covenant on Economic, Social and Cultural Rights (ICESCR). Article 15 the also confirms the right of everyone *"to enjoy the benefits of scientific progress and its applications"*. The valuable addition in the articles is that albeit this is a right; it is dependent on available resources, i.e. we have here a conflict between a state's equity and efficiency objectives (UN. Committee on Economic, 2011).

Often in the discussions about priority setting in public healthcare, when facing the subject of offering access to beneficial yet costly treatment, we look to the rule of rescue (RR).

The term was coined by Albert Jonsen (1986) and he describes the principle as follows; "*Our moral response to the imminence of death demands that we rescue the doomed. We throw a rope to the drowning, rush into burning buildings to snatch the entrapped, dispatch teams to search for the snowbound. This rescue morality spills over into medical care, where our ropes are artificial hearts, our rush is the mobile critical care unit, our teams the transplant services"*. This statement shows that it is not actually a *rule* per se, but it is describing our emotional reaction in the case of tragic events.

For us to apply the rule of rescue argument several criteria's must be met. The reappearing criterions seems to be that the patient must be identifiable, in the risk of death or disability if we do not intervene and lastly that there is an available intervention. All of this is criterions are mostly met when dealing with rare diseases. The exception being, that in many cases an available intervention as it often is not available due to lack of medical knowledge. We should from the RR perspective help the individual no matter the cost when these criterions are met. The RR viewpoint however challenges and contradicts the view of the standard cost-effectiveness analysis. It also overlooks the fact that the entire healthcare system is based on rescue; and that when someone is prioritized, health services must forego for others.

Neither of the mentioned theories focuses on that rarity should matter more than other criteria-but the focus is on that everyone in need of it, should receive help regardless of the

cost. Since the rule of rescue essentially gives added value to the identifiable as opposed to statistical lives, it is often considered together with the identifiable victim effect.

There are numerous examples around the world on how people are affected by the identifiable victim effect. The term is used to describe how people usually are more willing to help patients when they are presented to us as an individual rather than an anonymous case (Ritov & Kogut, 2017). Ariely (2008) describes our response to it as follows; "*This means that our feelings will not be based on their objective level of tragedy but instead on the way in which they invoke emotions in us".* How our feelings are affected may however or should maybe be morally irrelevant when it comes to allocation of scarce resources, as it will always come a new case where we would sympathies. As stated by Verweij (2015 page 138): "*if we are looking for a moral justification for the rule of rescue, appealing to sympathy cannot be enough".* This is not saying that sympathy should be disregarded altogether, as this is a typical human response but describes how if sympathy would be our only criteria, the allocation would often seem arbitrary.

Media has shown to have a big impact in identifying patients, as they offer us the stories that makes us as a society more likely to engage in the reimbursement discussion. We saw for instance in Belgium in 2013, that the reimbursement of Soliris® (Eculizumab) used for a rare autoimmune disease was approved after the producer leaked to the media that it would not be reimbursed. It is believed that the media focus was partly what changed the decision (Picavet et al., 2014).

Several other studies contradict this hypothesis on the medias impact however, as Wiss and colleagues (2017) showed in a survey of the Swedish public. They showed that when faced with an identifiable victim, the public was more likely to prefer to reimburse the more common disease. Wiss et al. (2017) did not explore why this was the case, and this could be an area for further research.

Their research showed nevertheless that different psychological factors such as educational level were an important factor when deciding, and that those with lower levels of education were more likely to prioritize rarity. When accounting for such factors, the preference for rarity is still below 50%. The educational level of the respondents has also been seen in Canada a few years before being an influential factor in prioritizing. The more educated

respondents[2] were here assumed to be able to look beyond the "newsworthiness" of an identifiable patient, and consider more scenarios to a higher degree than those with lower education (Dragojlovic et al., 2015).

Utilitarianism that is another branch of ethics regarding decision-making opposes the view of the identifiable victim effect on the basis that the public appeal of known lives should not be worth more than that of unknown lives (Silva & Sousa, 2015). Further, the utilitarianists dispute the rule of rescue principle as it often does not focus on opportunity cost and CEAs which assumes that the distribution of QALYs among the population is unimportant (McKie & Richardson, 2003). McKie and Richardson (2003) argue further that by letting the attention from the media dictate health care priorities, it would lead to adverse effects for the overall health in the long run. They claim this as the "newsworthiness" offered by individuals might not provide the most utilities for society. If we consider that we are faced with scarce resources, the utilitarianists make a compelling case on why we should disregard bot the rule of rescue and identifiable victim effect.

An often-used argument is that orphan therapies should not be funded through the public purse or private health plans because a patient with a rare disease requires more than their "fair share" of a limited health care budget. Fairness requires that we do not discriminate between individuals on morally irrelevant grounds, and the identifiability of some patients is such a ground, according to McKie & Richardson (2003).
On this; professor in health economics Bjarne Robbestad states, that patients should not be receiving more expensive treatments based on that they were "lucky" to get a rare disease (Bordvik, 2013). This is typically the Utilitarian approach; defined as when the outcomes determine the means and greatest benefit expected for the most considerable number of people (Mandal et al., 2016). This is also known as the consequentialist approach since the outcomes determine the morality of the intervention.
We can however, look at it from a different point of view; is it fair that patients with a rare disease should be punished and receive a lesser treatment just because they were unlucky to get an uncommon disease? This persuasive argument is coined the "double jeopardy" argument and was developed by Singer et al. (1995). It states that those who have already experienced significant disadvantage in their health state should not have further misfortune imposed upon them because their treatment is not considered cost-effective. We can further

[2] Lower education was in this case considered as not having a university degree.

say that rare disease patients are in a disadvantage not only because they have an uncommon disease, but also because there often is not an appropriate treatment, and it often takes several years for the right diagnosis to be set. Lastly, the rare disease patients and their families are in disadvantage by often not being able to work due to limitations or time used for informal care, and it has been estimated that families of patients with Duchene Muscular Dystrophy (DMD) would incur $15,481 a year in lost income (Larkindale et al., 2014).

It is a common opinion that benefits for those worse off should account for more than those who are better off. This view is coined as a prioritarianism point of view. Some may therefore, consider those with a rare disease as worse off since they have a limited number of available treatments (Herlitz, 2018). Others again would argue that when applying the prioritarianism view, we are confusing rarity with severity and that rarity does not automatically equal the worst off.

If one were to prioritize those that are worse off, we need to define what constitutes worse off. If one were to look only at QALYs achieved through a lifetime; men would according to British economist Alan Williams have to be prioritized in general, as they have a lower life expectancy and hence a lower level of QALYs on average (Williams, 1997). His argument shows that to achieve the highest overall utility, we may encounter unforeseen flaws in the argument. For instance; one might support the prioritarianism and utilitarian point of view, but most would consider this discrimination against women as unfair. Many would feel that this discrimination goes against their morals and would hence oppose Williams (1997) argumentation. When faced with dilemmas like this; we can say we are in line with Rawls (1971) third principle, the principle on reflective equilibrium. We have a moral "starting point" with normative positions and attitudes. From this starting point, our thought process moves back and forth from the starting point and our believed idea of fairness.

The fact that we should act in a way that offers the most utilities is nonetheless an often-used argument and especially important when dealing with a taxed based health system as is in Norway. Many believe that the public should decide how their money is spent as we are the one who pay. In terms of economic theory, this reflects an extra-welfarist foundation. The term extra welfarism tells, among other things how decisions made within a society should be made by a decision maker chosen by a socially approved political process (Sugden & Williams, 1978).

This way of thinking, and reimbursement to the larger groups, although damaging for some, would lead to a higher level of QALYs achieved in total from both a healthcare and societal perspective. The argument that the payers should decide becomes extra valid if we contemplate that society often pays twice for the drugs offered to us. First through R&D, which is often funded from state, i.e. tax money. The International Rare Diseases Research Consortium (IRDiRC) found for instance that 52 % of R&D was funded through governments (Dawkins et al., 2018). Secondly, we as consumers pay again, when we need to purchase the drugs from the pharmaceutical company.

Another argument against funding, or prioritizing rare diseases economically is that it has been shown in a Norwegian survey that doctors prefer to favor common diseases when deciding on what should be reimbursed (Desser, 2013). The doctor's views should, according to scholars count for more than the general public as they can make a more informed decision due to their medical education and that they are in general more used to making ethical considerations (Karnam & Raghavendra, 2017). This argument is also in line with the research conducted by Dragojlovic et al. (2015) and Wiss et al. (2017) as they showed that the public was inconsistent dependent on education in what should be the focal point in reimbursement decisions.

This asymmetry of information between the medical community and the people may be a compelling argument for the doctors to decide instead of the public, but here again, we need to look to the public as they are the payers.

The general public, however, is inconsistent when deciding if rarity should be a criterion when deciding reimbursement decisions. In previous research by Desser and colleagues (2010), the public stated in a survey that they agreed to the statement "*all individuals should have equal access to health care regardless of the cost"*. Further, they highly agreed that "*patients with a rare disease should have the right to treatment even if treatment is more expensive"* compared to a more common one. The inconsistency was nevertheless apparent as the public also said, *"health authorities should use resources to provide the greatest possible health benefits".* The last statement clearly contradicts the previous ones. Nonetheless, the survey may not be enough to conclude; as we know, people tend to have an inherent aversion against choice, so this may have biased their response. Further, the individual's risk aversion was not explored in the survey, nor their health state. These are two factors that may shape our preferences when deciding on reimbursement (Decker & Schmitz, 2016).Because of the

public's inconsistence, a natural sub question to explore becomes what the public in fact value.

3.0 RESEARCH METHODS

The purpose of the social sciences is to contribute knowledge on how reality looks in different contexts, and this knowledge requires using scientific methods. This entails that one uses a specific plan – a research design. The research design describes *who* is to be researched, *how* we are to gather this information, *how* we should analyze this information and finally *what* this information tells us about our research topic (Johanessen, Tufte, & Christoffersen, 2016).

3.1 The research questions

My research question is as described in the introduction threefold as it consists of *what* the thresholds are, *how* one argues for the different thresholds, and *what* consequences it may lead to.

When it came to the thresholds, as I said, I wanted to summarize what constitutes as a rare disease in selected countries around the world. I also looked to whether they had a national definition and a legal framework for it. In the cases an official threshold did not exist, I looked to if there was an unofficial one provided, for instance on provided by a patient organization.

The countries I was able to find a threshold on, is presented in the appendix. I chose to look at some of these countries in dept, and they are presented in table 1.

I chose to explore those countries in table 1 because these were the ones that provided the most information in both governmental sites but also there was written extensive papers on them. These countries were also all in the category lower middle to high income countries. An advantage by selecting countries within the same income groups were that they are more comparable in both availability to drugs, but also purchasing power. To identify the different income groups, I looked at how the World Bank Group (WBG) choses to categorize the different countries based on Gross National Income (GNI). Taiwan is not included in the table as it is not listed as a separate country by the WBG, but they are considered a high-income country by the UN (2019). The WBG definitions are provided in table 1 provided below.

World Banks categorization	Countries within this category
Lower middle income (GNI per capita between $996 - $3,895)	Philippines
Upper middle-income (GNI per capita between $3,896 - $12,055)	China Bulgaria (EU) Malaysia Romania (EU) Russia
High income (GNI per capita > $12,055)	Australia Canada US Japan Norway The remainder of the EU countries

Table 1: World Banks categorization

Source: The Word Bank. Numbers from 2018.

I was also especially interested in finding out if the thresholds were higher in the poorer of the chosen countries. This was a hypothesis I had, as one would assume, that these countries would have a lower PPP and that they therefore would have a lower accessibility to drugs. Although the countries in the EU are considered as a unit in my research, I do recognize that the different countries have a high degree of variation in gross domestic product (GDP). This is also apparent from table 1.

How one argues for the thresholds is interesting, as I wanted to explore whether they are chosen arbitrary or if there is a general pattern in the different parts of the world. I also wanted to see if there was a pattern of convergence throughout the years, as this was my hypothesis.

The ethics around the arguments were also a focus point. My hypothesis here, was that countries with a national healthcare system (NHS) were likely to have a more liberal threshold than those with private insurance systems. I believed this to be true, as countries with NHS often has a stronger welfare state. I recognize that countries such as Germany and the Netherlands display great signs of being focused on welfare although their system is based on a national insurance system.

As to the consequences of the threshold, I looked at both how the pharmaceutical companies react to the playing rules laid down by law, and if the threshold really matters when governments decides what drugs they want to reimburse, since in the end, it seems like the reimbursement decision comes down to a country's fiscal status. I lastly looked at the final question from another angle as well, if rarity does not matter; what does matter for policymakers and the public in the reimbursement decision?

3.2 Research design

It became apparent that the way to analyze my research questions was to look to and interpret the existing literature on the subject. The previous literature could provide me with a normative perspective from different viewpoint (Hanley & Winter, 2013). When one interprets previous literature, we say that this is a way of qualitative content analysis (Hsieh & Shannon, 2005).

I used a qualitative method since it focuses more on understanding opinions and its main purpose is to get descriptions and information on the research topic, in contrast to numbers generated by quantitative research (Green & Thorogood, 2018). Green and Thorogood (2018) further states that this is important in a health context as a qualitative method can give answers and understanding to questions that cannot be answered from a quantitative perspective. It is also stated that this method is preferred when the data can be put into words, but not numbers which is true when looking at normative data (David & Sutton, 2011).

3.3 Search strategy

Since a search on google for rare diseases provides over 355 000 000 results, I realized early on that I had to set different criterions when searching for literature. I decided to use a semi systematic literature review by using several different search words as shown in table 2.

List of key terms	
"orphan drugs"	"rare disease + threshold"
"laws + orphan drugs"	"EU regulations + orphan drugs"
"Incentives + orphan drugs"	"orphan diseases"

"rare diseases"	"market exclusivity"
"salami slicing"	"rare diseases + country in question"
"orphan drug +development "	"big pharma + loopholes"
"cost of health foregone"	"opportunity cost + drugs"
"neglected disease"	"rare disorder"

Table 2: List of key terms

We can say that it is a semi-systematic review since the search words were defined, but as opposed to a systematic review it did not involve a detailed and comprehensive plan and search strategy derived *a priori* (Uman, 2011)Secondly it differs from a systematic since it does not use data extraction tools to identify precise pieces of information (Duvendack, 2017)

An advantage by not having a strict plan, was that I was able to change direction based on what seemed fruitful as I went along (Robinson & Lowe, 2015). This way of research is often preferred when dealing with limited resources and time (Duvendack, 2017)

Further, I chose to do it semi systematic, since many of my sources may not be found in the conventional literature. Rather the documents, and especially the legal ones are dynamic and in constant change. Further, many of the sources stands from news articles and letters to the editor of different journals. A potential limitation with this method, is that I might have been biased when searching for literature, as I was not forced to consider all articles if they met my criterions.

Even though I did not have a fixed search strategy per se; I had several criterions when looking for literature.

3.4 Research criterions

First, I narrowed down my searches by only using trusted sites that is well known in the medical research environment (De Leo, LeRouge, Ceriani, & Niederman, 2006). The search engines I used are presented in table 3.

Search engines used	
Google	Google Scholar

PubMed	SpringerLink
ScienceDirect	MedLine
Ovid	Cochrane library
Nature	Drug Discovery Today

Table 3: Search engines used

Several criterions were further used when looking for articles. Among them were that the article should contain a full text, it should have been written in the last 10 years in those cases that it was deemed relevant. The articles should be open access, and lastly that they were written in Swedish, Danish, English or Norwegian. When it came to the legal documents, they were accessed from governmental sites to provide accurate information on any recent amendments. If this was not to be found, I looked to the *human rights library* a site provided by the university of Minnesota. When these criterions were added, the number of articles were decreased manifold.

As it has been concluded by scholars that using snowballing, as a strategy, may very well be a good alternative to the use of database searches I chose to continue down this path (Wohlin, 2014).

3.5 Snowballing

"Snowballing" is a way of reference tracking (Greenhalgh & Peacock, 2005). The term snowballing is used to describe how the search is emerging as the study unfolded. When exercising a snowballing method, the first challenge is to identify a start set of papers to use for the snowballing procedure (Wohlin, 2014).

I scanned the reference lists of all the papers that met my criteria and reviewed the abstracts of the potentially relevant papers from my database searches. I further used judgement to decide if I considered them to be useful. If so, I continued reading the newfound article. This way of using the reference list is defined as "backwards snowballing" (ibid).

One advantage of the snowball method is that I was able to find a lot of literature about a subject quickly as the literature grows at an exponential rate quite easily (Lecy & Beatty, 2012). The main disadvantage of this method is that when searching retrospectively, each

source will be older than the previous on. Here I once again looked at the time of publishing as a criterion.

For general information on what a rare disease is, I used the site Orphanet which is a site that contains information on rare diseases worldwide. Orphanet was established in France by the INSERM (French National Institute for Health and Medical Research) in 1997.This initiative became a European endeavor from 2000, supported by grants from the European Commission (Orphanet,2019).

For further information I used the database of the National Organization for Rare Disorders (NORD). NORD is a union of individuals, voluntary agencies and other health related organizations dedicated to helping patients with rare diseases. I also used the page EURODIS, which is the European Rare Diseases nonprofit organization.

I also frequently used the site Kaiser Health News which *is a nonprofit news service covering health issues in the US.*

I also used several official governmental sites for the country specific information regarding thresholds and laws. For more general information on the EU member states, I used the European Union's official site.

4.0 RESULTS

In this section, I will present my findings from the research, both in the case of what the thresholds currently are, what the argumentations for them are, how they are evolving ,what incentives are needed to produce orphan drugs, how the pharmaceutical sector adjust to the legal framework and lastly what the public values in a reimbursement decision.

4.1 Different thresholds exist

The definition of a rare disease is as shown broad, but this does not mean that it is universal, different countries consider different thresholds to qualify a disease as rare. The World Health Organization (WHO) has suggested to make a universal threshold of 6.5 patients out of 10000 (Aronson, 2006). They have to this date not been able to do so, and according to scholars, this is too high with the argumentation that it does not capture what is truly rare (Aronson, 2006).

It is estimated that the thresholds vary as much as 0.18-7.5 per 10 000 population in different countries (Christopher McCabe, Claxton, & Tsuchiya, 2005). The global average is according to Richter et al. (2015) 4 cases per 10.000.

In the table 4 below I have summarized the information I gathered about the thresholds of the key countries in this study. They are in focus as they were those countries, I found the most information about after an extensive search. The focal point was also to include both low middle-income, high middle-income and high-income countries. I chose to not include the low-income countries as they do not have the funds to buy orphan drugs, so in the case of a threshold; it would not have implications in practice. The Scandinavian countries are chosen because even though they are a part of the EU (with Norway being the exception), they operate with a different threshold than other member states.

Country	Threshold	year of legislation	amended legislation
The EU*	5:10000	2000	
US*	7.5:10000	1983	1997
Canada	5:10000	N/A	

Taiwan**	1:10000		2000	
Philippines***	0.5:10000		2016	
Japan*	4:10000		1993	2017
Malaysia******	2,5:10000	N/A		
Russia****	1:10000		2011	
Australia*****	5:10000		1989	2017
Norway	1:10000	N/A		
Sweden	1:10000	N/A		
Denmark	1-2:10000	N/A		

Table 4: Different thresholds of selected countries

Sources: *(Mariz et al., 2016)(. **(P. Song, Gao, Inagaki, Kokudo, & Tang, 2012), ***(Rare disease act of the Phillipines,2016), ****(EUCERD, 2014) ***** (HealthyWa, 2019),*******(Chu, 2019)

4.1.1 How has the thresholds evolved and what were the argumentation?

As shown in table 4 above several thresholds exist. I will in this section describe how the thresholds has evolved through the years. I will also look at different arguments for the thresholds and the evolution of them. The thresholds are important to understand, as they often affect reimbursement and policy decisions.

The USA were the first country to define a threshold in 1983 after pressure from interest organizations such as the National Organization of Rare Disorders (NORD), and several different thresholds have circulated since then (Rhee, 2015). The Rare Diseases Act of 2002 defines a rare disease as having a prevalence of no more than 200 000 affected individuals in the United States, or no reasonable expectation of being profitable (PUBLIC LAW 107–280—NOV. 6, 2002) . This would equal to approximately 6 in 10.000 people when we look at their current population (Heiberg, Frich, & Røttingen, 2014). OrphaNet (2019) however states that the US threshold is closer to 7,5:10000. There threshold is rumored to have been decided during a discussion in a U.S. Capitol bathroom between Abbey Meyers and Dr. Marion Finkel, the first leader of the FDA's orphan drug initiatives (Kopp, Lupkin , Tribble, & Zuraw

2017). It is also said that the threshold is arbitrary and based on the estimated prevalence of narcolepsy and multiple sclerosis in 1983, both diseases the pharma companies were not willing to manufacture drugs for at the time (Aitken & Kleinrock ,2017). Current estimations do however calculate that these diseases are below and above the threshold respectively. Nevertheless, how it was decided; the US has not amended their threshold since it was defined, but they did amend their incentives for production of orphan drugs in 1997. Based on their stated threshold, there are approximately 25 million US citizens suffering from a rare disease (Graf von der Schulenburg & Frank, 2015).

Australia was only a few years behind the US to develop a threshold. Australia originally operated with a threshold of >2000 patients to define a disease as rare. This threshold was developed in The Therapeutic Goods Act (1989) Regulation 2- the equivalent of approximately 1 patient in 10,000 persons[3]. As population rose, this definition became one of the strictest among the high-income countries, as it in praxis meant less than 0,8 in 10000. The chosen threshold was heavily criticized by the public for being too rigid and not in line with population growth, and therefore it was amended in 2017. Now the health department of Australia defines a disease as significantly rare when it affects less than 5 in 10.000 (HealthyWa, 2019). This is the same definition used by the EU. Although not stated, it is assumed the EU was the pioneer when amending the threshold. The Australian health department stated that; "*Changes to the program were implemented to create a fairer program that aligns more closely with international criteria without impeding the availability of drugs for rare diseases"*(TGA, 2018).With their new definition of 5:10000, there would be approximately 1.2 million Australians affected by a rare disease.

Japan was the second country in Asia to define a rare disease threshold (second only to Indonesia) (Shafie et al., 2016). In Japan, the prevalence must be less than 50 000 people (.05%) on the Japanese territory to consider a disease as rare, which corresponds to a maximal incidence of four per ten thousand. (OrphaNet, 2019). This was stated in Article 77-2 of the Pharmaceutical Affairs Law, from 1993. From 2017, Japan's ministry of Health, Labor and Welfare (MHLW) expanded their threshold from diseases with less than 50,000 patients to less than 180,000 patients if the disease were considered a "nanbyou[4]" in 2015 (PacificBridgeMedical, 2017). A disease is referred to as Nan-Byo if it is a rare disease of

[3] The equivalent of 1 in 10,000 persons is commonly referred to in terms of Australia's rare disease definition. Updating for current population this would be closer to 1 in 11,500 persons. Geoffrey K. Herkes (2016) Orphan drugs in Australia, Expert Opinion on Orphan Drugs, 4:12, 1195-1197, DOI: 10.1080/21678707.2016.1257383

[4] Defined as designated intractable disease i.e.

unknown etiology which requires currently unavailable treatment measures and long-term care for the patient (Adachi et al., 2017).

In Canada there still is not a legal framework as of 2019 in contrast to the other high-income countries, despite several attempts for developing it. The first proposed policy was rejected in 1997, on the basis that there had not been significant pressure from interest groups. Another argument used was that orphan drugs were accessible to Canadians from other countries with their current legislation (McMillan & Campbell, 2017). If this were the case is debatable, since it has been shown that in 2014, only 60 % of the approved orphan drugs in the EU and US gets approved in Canada, and their approval is often up to six years later than the EU and US according to the Canadian organization for rare diseases (CORD) (NP, 2014).

The Canadians was supposed to develop a definition on rare diseases in 2017, but the Canadian government has later removed all information on the topic on their homepages. This has been heavily criticized by the public and Durhane Wong-Rieger, the president and CEO of CORD stated that the decision "*certainly seems to be the kiss of death"* for the proposed orphan drug framework (Forrest, 2017).

Due to the lack of framework, provinces within Canada have developed their own systems for orphan drugs, with varying degrees of success (Menon, Clark, & Stafinski, 2015). Since Canada lack a formal framework, it is not as easy to see what influences the reimbursement decision on orphan drugs, and they currently consider applications on a case to case basis (Hall & Carlson, 2014). Rosenburg-Yunger et al (2011) found in their research that the Canadian government often use the rule of rescue as a criterion, a concept described heavily in the theoretical framework. The rule of rescue was for instance used as the argument when a treatment for Gaucher's disease was funded after a media outcry led by the National Gaucher Foundation of Canada after it was initially denied reimbursement (Clarke, Amato, & Deber, 2001). Dragojlovic and colleagues (2015) believes this a suboptimal way for policy makers to decide. They have shown in their research that the public is inconsistent in how they value rare diseases when it means that the budget for common diseases must be decreased.

In Europe most of the 28 countries in the European Union has the same definition. In the EU the definition of a rare disease is having a prevalence of not more than 5 in 10 000. This definition first appeared in EU legislation in Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal product. The existing definition of rare diseases in the EU was adopted by the Community action program

on rare diseases 1999-2003 (ibid). With the threshold in use, it is estimated that between 27 to 36 million Europeans are affected by a rare disease (Graf von der Schulenburg & Frank, 2015).We know that there is a large homogeneity in the disorders in the EU, since according to the European Medical Agency (2019), most people suffer from diseases affecting fewer than 1 in 100,000 people.

The Scandinavian countries are interesting as they of 2019 have circumvented the threshold laid down by the EU. Norway, Denmark and Sweden currently have about the same threshold, a threshold five times stricter than the one in the EU. Norway has not set their threshold based on an incident percentage, but states that when less than 500 people has the disease, it is considered rare regardless of the size of the population (Meld. St. 34 (2015-2016), 2017). Norway's center for rare diseases (Nasjonal kompetansetjeneste for sjeldne diagnoser ,NKSD) state that Norway considers a disease as rare when it is less than 100 people per million are affected, and this number is also approximately 500 people (NKSD, 2019). In other words, Norway's threshold is not defined as an absolute number (Heiberg et al., 2014). Norway were supposed to come up with an updated definition in 2018, but the decision has however been postponed. The argument for the delay, is that the Norwegian government wants to see if Sweden chooses to update theirs according to the EU standard (Storvik, 2019). The director of the Norwegian department of disability's in the health directorate Lisbeth Myhre are however arguing against the EU definition, as it does not show what she defines as rare diseases (ibid).

As of now, we can say that although the threshold in Sweden and Norway are the same; Sweden is somewhat stricter since they also state as a criterion that the disease should lead to severe disability (RiksförbundetSällsyntadiagnoser, 2019). Denmark does not have a clear-cut definition either, and often says that a disease is rare if it affects between 1-2:10000 (NNRD, 2018). Rare Diseases Denmark (Sjældne Diagnoser Danmark,2019) states that 2:10000 is their definition. We can see a common trend with the definition offered by rare disease Denmark; it is on the more liberal end compared to the more "official one". When deciding on reimbursement Denmark are also quite like Sweden as the general rule is that the disease must be severe, genetic or congenital (EUCERD, 2012).

Russia has a quite strict definition, and rare diseases are defined as affecting no more than 1 case per 10 000 inhabitant (EUCERD, 2014) .This was stated in article 44 in the Federal Law on the Foundation of Health Protection in Russia, 323-FZ from Nov 21, 2011.

Taiwan also operates with a threshold of 1:10000 to consider a disease as rare. Their legislation on rare diseases (Rare Disease and Orphan Drug Act, 2000) came in January 2000 after several patient organizations, society and medical professionals lobbied for it (Hsu et al., 2018). Between 2003 and 2014, the prevalence of rare diseases increased 3.14-fold in Taiwan. It is believed that this is not an actual increase in prevalence, rather the estimations are higher due to a bigger focus on rare diseases and screening for them since the legal framework came (ibid).

The Philippines has a threshold of 1 case per 20000, in standardizes numbers like the others presented this would equal to 0,5:10000. This was defined in the Republic act NO 10747, or the Rare Diseases act of the Philippines (2016) . The Philippines differs from other countries as they after 2006 automatically consider a patient as disabled when they have a rare disease. This was an amendment in the Magna Carta for disabled persons, a law for disabled's rights ("Magna Carta for Disabled Persons REPUBLIC ACT NO. 7277," 1992). This is the opposite to other countries who often specify for a patient to be disabled or in the risk of becoming *before* qualifying for a rare disease status.

Malaysia is among those countries who does not have an official threshold from a governmental side, but the Malaysian Rare Disorders Society (MRDS) has set the threshold of 2.5 cases per 10.000 (Chu, 2019). The Malaysian National Medicines Policy 2012 (second edition) states that when it comes to orphan drugs *"there shall be appropriate procedures to enhance accessibility to life-saving products and orphan drugs without compromising safety, quality and efficacy".* As the government has not defined what constitutes a disease as rare, or orphan, it is hard to interpret this statement. The Malaysian government were to develop a national framework for rare diseases and orphan drugs they stated in 2017. To this day, they have not done so yet. Further, they offer no financial incentives to produce orphan drugs (PacificBridgeMedical, 2017b).

China is also among the countries that has not set a legal threshold, but it is suggested that the government considers it to be 1:500000, or 1:10000 in newborns (Cui & Han, 2017). Cui and Han (2015) however suggest that the threshold should be 2–4 out of 10,000, based on the Chinese population of 1.35 billion.[5] They considered this too be comparable to the EU and the US when population size is considered (2015). WHO again argues that China should use their suggested definition of 6.5 out of 10000. The suggested WHO threshold would mean

[5] Population in 2015

that at least 10 million people in China are living with a rare disease (Wang et al., 2010). Despite the lack of a formal threshold, China do however have a national list of what they consider to be rare disease developed by the *Expert Committee on the Diagnosis, Treatment, and Care for Rare Diseases* established by the Medical Administration Bureau of the former National Health and Family Planning Commission (He, Kang, Hu, Song, & Jin, 2018).This list contains 121 diseases, i.e. far from all identified are included.

4.1.2 What are the common factors?

After looking at how countries choose to define the threshold for rarity it seems quite arbitrary. The country with the strictest threshold in the world is for instance over 40 times stricter than those with the most liberal threshold. Other authors also support this finding and according to Ritcher.et al (2018) the thresholds are decided on an arbitrary incidence rate.

We can see that the thresholds are becoming increasingly convergent. Most developed countries have about the same threshold in prevalence and it was developed around the same time. A common difference is that different countries vary if severity and the possibility of disability should be considered. Canada is a clear exception among the high-income countries I explored as they still have not developed a legal framework.

Many of the countries who either does not have a threshold, or currently have a strict one is considering too changing theirs to the EU standard, Norway and Sweden is as explained examples on this.

The EU standard is also used in several countries unofficially. An important finding is that those countries who uses the EU definition unofficially, is often high-income countries with national health services (NHS), this is according to my hypothesis regarding welfare states. The literature somewhat supports this view as some papers has shown that on average, countries with private payers had the lowest average threshold at 1.8 cases per 10.000 inhabitants (Richter et al., 2015). The most liberal, but then again unofficial thresholds are provided by patient organization with a global average of 4.7 per 10.000 inhabitants (ibid).

Another meaningful finding is also that while the EU uses a set threshold that is not affected by increasing population, many Asian countries has a threshold that is coined in a way making it stricter as population size increases. Further, the Asian countries are in most cases stricter than the EU on what a qualifies as a rare disease. Taiwan is one of the countries that

contradicts my hypothesis on NHS and thresholds, as 97% of the population is included in NHI schemes, and they are considered a high-income country, but their threshold is still quite strict. The most surprising discovery is how arbitrary these thresholds are in general. After the one in the US was defined, most countries circled around that same threshold.

4.2 Economic implications of the threshold

As I have now shown, the thresholds are not the only thing that differs between the countries. They also have different rules and laws about the implications of the definitions, for instance on incentives for orphan drugs, pricing and research and development. The thresholds also have different background histories and reasoning behind the rules. In this next section I will explore this in more detail in order to examine whether there are any systematic patters between the countries. First, I will describe why the high cost of orphan drugs are shown to be a problem and secondly, I will explore the legal framework in the different countries with focus on the different incentives offered to produce orphan drugs.

As previously stated, orphan drugs are in most cases not considered to be cost effective regarding each quality adjusted life year (QALY) they provide with the cost of providing them. I will in this section describe and discuss why the lack of such effectiveness is an increasing problem with orphan drugs.

The high cost of the drugs might not have been a problem previously when orphan drugs were rare. When they were rare, the healthcare systems were to a large degree able to deal with them in an ad hoc manner when faced with the reimbursement question (Christopher McCabe et al., 2005). The problem of the high cost is however increasing since we are now able to identify a potential treatment for a larger proportion of the rare diseases. If one were to look at the total use of resources within one disease, the cost may still not be substantial, but since there are up to 8000 rare diseases it may now account for much of the budget impact in total.

It is estimated that as many as 400 million people worldwide are rare-disease patients (Graf von der Schulenburg & Frank, 2015).If one were to reimburse for all of them, the total cost may lead to fiscal unsustainability. In 2016, the median annual cost for an orphan drug was over $32,000 per year (Aitken & Kleinrock, 2017)

It has also been estimated that by 2030 *"specialty pharmaceuticals will account for up to 44 % of a plan's total drug expenditures"* (Sullivan, 2008). According to a report from

Deloitte (2019) orphan drugs sales will total 216 billion USD in 2022, up from 217 billion USD as it were in 2017. Orphan drugs now account for seven of the 10 top-selling drugs of any kind, ranked by annual sales, according to EvaluatePharma (2019).

Further when looking at costs, we need to look at the opportunity cost; that is defined as the cost of a benefit that must be forgone in order to pursue a better alternative (Becker, Ronen, & Sorter, 1974). In our case, as in all with scarce resources, the funding of orphan drugs would lead to that another treatment would go without funding.

Some argue that in the UK*, £2.5 million spent on orphan drugs (say 15 patient-treatment-years at £160 000 annually) would pay for over 520 hip replacements* (C. McCabe, Tsuchiya, Claxton, & Raftery, 2006).

Still it is important to recognize that increased use of available orphan drugs may reduce the need for hospitalization among many patients. A study from Western Australia concluded that in 2010 the state population affected by a limited cohort of only 467 rare diseases represented 2% of the population but 10.5% of in-patient hospital costs (Walker et al., 2017).These are costs that could have been avoided to some degree as has been shown by several studies (Lichtenberg, 1996). Absenteeism and/or limitations in the workplace may also be reduced with the use of drugs and hence lead to increased tax revenue from both patients and caregivers (Morel et al., 2016; Shire, 2013). Further, the use of formal and informal care may be reduced, and the quality of life (QoL) may be increased in both the caregivers and patients (Angelis, Tordrup, & Kanavos, 2015).

4.2.1 Incentives to produce orphan drugs

As stated, the small patient groups make it less attractive to produce orphan drugs, as there is a limited sales potential, and as like all other drugs, there is a high risk involved in the production. We know from microeconomics that several conditions are required for a perfect market to exist (Stiglitz & Walsh, 2006). The healthcare and pharmaceutical market fails to meet these conditions since it among other things consists of negative goods, i.e., goods we would not purchase if we did not have to. Secondly, there is a high degree of asymmetric information (Sloan & Hsieh 2012).

These are factors that fundamental economic theories state would lead to market failure if the government did not get involved (I, A.H, & Juni, 2018). Since we cannot decide the

prevalence of orphan diseases, the demand side of the drugs is out of our control. Therefore, we need to look at the supply side of the market i.e., what the pharma sector offers the consumer. Because there is a societal need to provide these drugs, the pharmaceutical sector is now offered more incentives to produce them. The incentives may be both financial such as research grants and tax exemptions and non-financial, such as fast track approval and advice (Gammie, Lu, & Babar, 2015).

4.2.2 Incentives in different countries

As shown, offering incentives are essential for the industry to produce the orphan drugs society needs. In this section, I will present the different incentives offered in different countries.

Since the US is both the most significant drug maker and the largest single drug market in the world, it is not astonishing that they were the first country to incentives the production and marketing of orphan drugs (Petsko, 2010; Rodriguez-Monguio, Spargo, & Seoane-Vazquez, 2017). The US developed the orphan drug act in 1983 (ODA). The act is considered a success since it has led to many new drugs entering the market. Before the Orphan Drug Act was established, only ten orphan drugs were approved in the decade prior. In 2017, 34 years after the ODA, a total of 451 drugs had been approved (Lanthier, 2017). The numbers may still be misleading, as it does not differentiate between new orphan drugs and older drugs who later received orphan drug designation. It is nonetheless estimated that orphan drugs will account for 19 percent of the total prescription drug spending by 2020 in the US (UNESCO, 2015)

One of the main incentives the pharmaceutical companies are offered in the act is a seven-year market exclusivity. This market exclusivity is different from a patent as it starts when the drug receives market authorization from the FDA, whereas the patent is applied for and received in the development phase of the drug (Sarpatwari, Beall, Abdurrob, He, & Kesselheim, 2018). This market exclusivity forestalls marketing approval of a generic drug or brand name for the same rare disease indication even when the patent has expired (Gammie et al., 2015) . Sarpatwari and colleagues (2018) found for instance that this was the case in 18% of the approved orphan drugs between 2005-2014. The fact that generics are forestalled is a vital incentive as pharmaceuticals are not affected by brand loyalty like other products ,i.e. we would change to a cheaper alternative if possible (C. P. Miller, 2012)

The ODA also offers tax credits. The Orphan Drug Tax Credit (ODTC) gives a 50 % tax credit on research and development costs. A study conducted by EY (2015) has concluded that as many as one-third of orphan drugs would not have been developed had it not been for the tax incentives offered. The ODA also offers grants for conducting clinical trials.

The orphan drug act was amended in 1997 and added a waiver of drug application fees to the Food and Drug Administration (FDA)(A. Kesselheim, 2010). Until 2016, the orphan drug applicants were review in 90 days, it has now been increased to 120 days as the FDA has seen a doubling in applications (FDA, 2017). The US government is now working on reducing this period down to 90 days again.

Japan followed the US in 1993, and they offer in their orphan drug legislation ten years of market exclusivity and financial subsidies for up to 50% of expenses for clinical and non-clinical research during the entire research process. Thirdly they offer 15% tax credits on research costs excluding financial subsidies, and lastly up to a 14% reduction in corporate tax (P. Song et al., 2012). Since 2015 they have also been trialing its "Sakigake", an accelerated approval scheme for innovative medicines (Deloitte, 2019). Japan differs from many other countries, as they specify in their legislation that when a drug reaches blockbuster status (profits exceed 100 million yen), pharmaceutical companies are required to pay a 1% sales tax to offset the subsidies they received from the government (Patel, 2017; Peipei Song, Tang, & Kokudo, 2013).

In Australia, R&D is not supported by grants or tax incentives on a national level, according to OrphaNet (2019). On a national level, they offer a 100% fee waiver on evaluation, and the Therapeutic Goods Administration covers the orphan drugs registration fees. Pre-licensing access and Regulatory Assistance is also offered (Barak & Shankar Nandi, 2011). Albeit the incentives on a national level are not grand compared to other countries with approximately the same Purchasing Power Parity (PPP), some jurisdictions have extended their support. They are providing tax benefits, increased periods of market exclusivity, and grant programs for the development of drugs for rare diseases (TGA, 2015).

The European Union came in 2000 with the: The Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

Regulation (EC) No 141/2000 offers ten years of market exclusivity as it has been claimed to be one of the most attractive incentives for the pharmaceutical sector. Two additional years of

market exclusivity is also offered if the drug is intended for pediatric use (Giannuzzi et al., 2017). These additional years seem to be attractive as about 60% of orphan designations in the EU are intended for pediatric use (EMA,2019). An important difference from the ODA is however that Article 8(2) of the Regulation specifies that the market exclusivity may be reduced to 6 years if the drug is sufficiently profitable after 5 years. What constitutes as sufficient earnings is not specified in the regulation.

Another important difference from the market exclusivity offered in the US, is that in the EU, the Regulation (EC) No allows for the entry of a non-similar product for the same therapeutic indication as an existing drug if it offers a significant benefit to patients suffering from the rare disease (Hughes-Wilson, Palma, Schuurman, & Simoens, 2012).

The regulation also offers access to the Centralized Procedure for Marketing Authorization as an incentive ("Regulation (EC) No 141/2000 ", 1999). With this accelerated assessment, the evaluation period is shortened from 210 days to 150. Further, the different member states may also provide various other incentives based on their national legislation (EC, 2016). The EU based their decision to provide incentives on the principle that;

…patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is, therefore, necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry… (European Commission, 2000).

From 2000 to 2011, more than 850 orphan drug designations were granted by the European Commission ,and more than 60 orphan drugs received marketing authorization by the European medical agency (EMA) (The Committee for Orphan Medicinal, the European Medicines Agency Scientific, & Westermark, 2011). Further, in 2017, one in five of new drugs to receive market authorization from the EMA was for rare diseases (Huuse, 2018). For a drug to fulfill the EMA's conditions of orphan drugs, it needs to be used for the diagnosis, prevention, or treatment of patients with a life-threatening or chronically debilitating condition (EMEA, 2017).

Market authorization from the EMA does however not guarantee patient access to any given drug (Blankart, Stargardt, & Schreyögg, 2011).We can state this since even though the members of the EU have the same legal framework, the reimbursement and decisions

governing pricing differ substantially as this is decided on a member state level (Simoens, 2011).

There is a difference in opinion on how many patients are offered available orphan drugs in the EU, but some claim that as few as 1% are offered approved treatments (Hughes-Wilson et al., 2012) ,others however states that there is as many as 10 % who do receive treatment (Melnikova, 2012). According to a study from 2018, the percentage of reimbursed orphan drugs varied from 27% in Poland to 88% in Denmark, with an average value of 51% ($p < 0.0001$) (Malinowski, Kawalec, Trabka, Sowada, & Pilc, 2018). This is an interesting discovery since Poland is considered a high-income country by the World Bank (see table 1).

The gross domestic product (GDP) and the availability of a formal health technology assessment organization within each country have however proved to be key differences in the uptake of orphan medicinal products in the EU (E. Picavet, Annemans, Cleemput, Cassiman, & Simoens, 2012). This is especially noticeable in eastern European countries (Zelei, Molnár, Szegedi, & Kaló, 2016). These countries, with an overall lower GDPs, is shown to have a higher median cost for treatments, i.e. they must engage more resources to provide orphan drugs for their population (Young, Soussi, & Toumi, 2017).

To increase their bargaining power against the pharmaceutical sector, several countries have founded groups that negotiate together. In eastern Europe, we have the Visegrad group that consists of Chechia, Poland, Hungary and Slovakia. In western Europe, we have the BeNeLuxAl collaboration, and for the southern European countries the Valletta Declaration (ibid).

In Taiwan, the Rare Disease and Orphan Drug Act (2000) offers several incentives for the development of orphan drugs. They offer grants, copay can be waived, fast track approval, protocol assistance, and medical reimbursement. Lastly, they offer a 10-year market exclusivity (P. Song et al., 2012). In Taiwan, the government has a reimbursement cap of 70% on medical expenses, but low-income families may be fully reimbursed for orphan drugs.

China has since 2009, offered a fast approval process for drugs to treat several rare diseases. This has only been semi-successful , since in 2016, only 37.8, 24.6 and 52.4% of orphan drugs approved in the US, EU and Japan, respectively, were available for the Chinese consumers (Gong et al., 2016). Jin & Chen (2016) argue that this is because the drugs has to be mostly paid out of pocket as it is not covered by standard health insurance. Because there is a lack of incentives, the pharma industry in China is not focusing on producing orphan

drugs. The health department has also from 2017 encouraged the pharma sector to provide "*drugs that have a significant clinical value in rare diseases*" by offering priority review (Deloitte, 2019). China offers no financial incentives as of 2019.

4.2.3 Common for all the countries

One thing that all the countries has in common besides incentives; they all accept lower levels of documentation regarding clinical trials when it comes to approving orphan drugs. The trials are often not doubled blind or placebo controlled. Lastly, they are usually not randomized clinical trials (RCTs) which is considered the gold standard, because there is a lower level of patient heterogeneity than in other diseases (Logviss, Krievins, & Purvina, 2018). This is partly since small patient groups, makes it hard to carry out trials on a large scale, often there is a lack of appropriate diagnosis and comparator (Dupont & Van Wilder, 2011; Rosenberg-Yunger et al., 2011). The comparator used is also in many cases old and without proven efficacy (M. F. Drummond, Wilson, Kanavos, Ubel, & Rovira, 2007). Furthermore, there are more ethical considerations that needs to be made since many of the diseases affect children regarding trials and consent (Caldwell, Murphy, Butow, & Craig, 2004). Gianuzzi et al. (2017b) also finds in their research that trials involving neonates are even more challenging economically compared to other trials.

The lower level of documentation required however affects the likelihood of the drug being approved. As highlighted by Deloitte (2019) the shorter trials may not adequately show the true value of the new drugs and they may therefore not be reimbursed. Reimbursement is also a common problem in low-income countries and those who does not have a national health system. The use of out of pocket payments are also often a reason orphan drugs are not accessible in many countries.

Another downside shown more frequently with orphan drugs compared to more general drugs, is that they may have a higher incident of safety issues. This is especially common if they have been fast-tracked (Heemstra, Giezen, Mantel-Teeuwisse, de Vrueh, & Leufkens, 2010).

4.3 Does the pharma industry adjust to the legal framework

As I have now shown, several different incentives exist to produce orphan drugs. This leads to the question if the legal framework currently in place encourages innovation and benefits the patient, or if it mostly benefits the pharmaceutical sector. In this section I will present different ways the pharmaceutical sector sometimes adapts to orphan drug legislation for their advantage. As the pharmaceutical sector to a large degree consist of commercial companies which are profit maximizing, it is not surprising that they adjust their tactics to increase their earnings (Reinhardt, 2001). There are concerns that the sector adjust by using loopholes in the orphan drug legislation to make the law work for them (Lainscak & Rosano, 2019).

They can use such loopholes as the law does not adequately distinguish between "true orphan drugs" and "Trojan horse" applicants that seek to reap the benefits for drugs that should not qualify as orphans (Gibson & von Tigerstrom, 2015).It has been claimed that a rep from a pharmaceutical company stated; *"we do not need new drugs, rather we need to find new patients that can benefit from our existing drugs"* (Lipinski, 2011). This statement can be interpreted in two ways; both how old drugs can benefit other patient groups, but it can also show how the pharmaceutical uses the drugs already on the market to increase their earnings. The latter is also known as both "evergreening" and "salami slicing".

4.3.1 Evergreening

One way the pharma sector is using the laws to their advantage is by so called evergreening. The term refers to how the pharma sector apply for orphan drug status on a drug already on the market to extend the life of a patent (Feldman, 2018; Mohammad Jafari et al., 2018). The pharmaceutical companies usually apply based on the discovery of new useful activity in an older clinically used drug that can be used for another disease, or another administrative method for the current drug. This leads to that some drugs may achieve multiple orphan drug designations and approved indications (Lipinski, 2011). By doing so, the pharma companies receive government incentives plus market exclusivity on each of their new indications. One of the more extreme examples of this practice may be the cancer drug Avastin who currently has 11 different approved designations (S Tribble & Lupkin 2018).

The pharma companies defend their practice by using the term "repurposing of drugs" rather than calling it "evergreening" and claim they offer hope to people who otherwise would not receive treatment (Bloom, 2016). This notion of hope is highlighted by Petsko (2010) who

states; *"Give me your tired, your poor, your Phase II failures… What if those drugs were not tried on the right disease? (...) What if the cure for Alzheimer's disease is sitting on some drug company's shelf, as a potential cancer drug that failed in Phase II? (...).*

They pharma companies also highlight how this practice makes it possible for drugs to access the market faster, since it has already shown that it is safe through previous RCT (Hernandez et al., 2017). This is known as *in silico* approach, that employ existing data to identify potential new drug–disease associations (Cha et al., 2018). Ashburn and Thor (2004) claims that the drug can enter as much as 5-7 years earlier than normal when repurposing previous research. This could greatly benefit many patients if the drug offers something new, as the average time it takes for a drug to come to the market is 12.5 years (Xue, Li, Xie, & Wang, 2018). Another way the industry adjust to the legal framework is by using a "salami slicing" technique.

4.3.2 Salami slicing

Salami slicing is defined in the medical community as when the pharmaceutical sector artificially subdivide diseases to create subgroups of patients that fall under the orphan drug prevalence threshold (Gibson & von Tigerstrom, 2015)

Regardless of how one chose to coin the concept of "salami slicing" The US government tried to protect against this when the FDA issued a rule in June 2013 that clarified its position: *applicants must provide scientifically plausible evidence for the uniqueness of a disease* (Reardon, 2014 page 17). The pharmaceutical companies can provide this evidence as the stratifying of genotypes in for instance cancers makes it possible to divide the patients in subcultures in a higher degree than before (Graf von der Schulenburg & Frank, 2015; Luzzatto et al., 2018) .This is often referred to as "precision medicine", and this contradicts in a way my previous statement that we are unable to control the demand side for orphan drugs (Li & Meyre, 2014; Lipton, 2003). The Obama Administration's further devoted 215 million USD for the development of "precision medicine" (House, 2015). In other words, the industry can make a common disease rare and they will receive funding for it. According to work by Kesselheim and colleagues (2017), this "supply induced demand" by "creating" more diseases is an increasing trend, especially in cancer diseases.

We saw this for instance in the US in the case of lung cancer drugs. Lung cancer is next to breast cancer the most commonly diagnosed cancer around the world, and it is the leading

cause of cancer-related death (WHO, 2018). In the US, Non-small cell lung cancer (NSCLC) accounts for 85% of the estimated 400,000 cases of lung cancer so it is considered as common, i.e. well above the US threshold of 200.000 (Molina, Yang, Cassivi, Schild, & Adjei, 2008). The drug Xalkori received in 2010 designation as an orphan drug since the biomarker status of the non-small cell lung cancer (i.e. ALK-positive, MET-positive, or ROS-positive) brought the prevalence below the threshold (Reese, 2015). Having said that, the use of biomarkers to tailor the treatment for NSCLC has proved to significantly improve outcome for patients (Korpanty, Graham, Vincent, & Leighl, 2014). Xalkori is not the only example; from 2009–2015, 16% of orphan-designated drugs were based on predictive biomarkers that made it possible to divide common diseases to rare subsets (Kesselheim et al., 2017).

Since the use of biomarkers to subgroup is especially common in cancer, the pharmaceutical sector in the EU has suggested that in the case of rare cancers, the threshold should be raised to 6 in 10 000 as up to 44% of orphan drugs are designated to cancer (Gatta et al., 2011; Rollet, Lemoine, & Dunoyer, 2013). This definition has not yet been changed, but it is an important question as it is expected that the prevalence of cancer will increase by 23 per cent from 2018 to 2040 (Bray et al., 2018). The use of biomarkers, also leads to an increased focus on how different races respond differently to medications (Grutters et al., 2013). Another way the pharma industry sub-divides in addition to the use of biomarkers are factors such as state of disease, age or the underlying cause of disease (Gibson & von Tigerstrom, 2015).

Some other examples of drugs already on the market that have used the method of "salami slicing" is the cholesterol blockbuster Crestor, Abilify for psychiatric conditions and the cancer drug Herceptin (S Tribble & Lupkin 2017). The rheumatoid arthritis drug Humira currently has 12 different indications, four of them under the ODA (Aitken & Kleinrock, 2017). We can therefor call Humira a "partial orphan drug," since it has both orphan and non-orphan indications (ibid). Partial or not, Humira is currently the best-selling medicine in the world

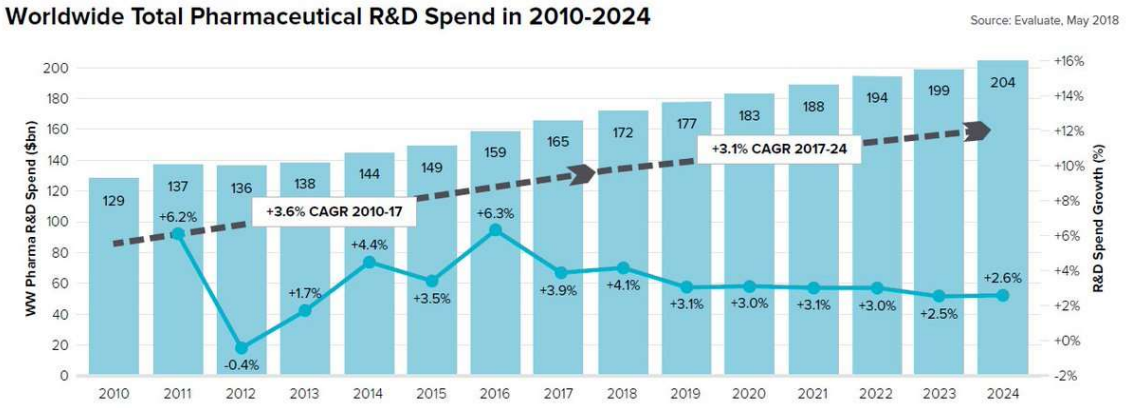
By using the salami slicing technique and evergreening, the pharma companies are not breaking the law, rather they are using the law to their advantage in a way that was not foreseen when it was developed. Critics against this way of conducting business does not only highlight the fact that the prices increase. Another often used argument is that this could lead to lack of research on "actual" rare diseases since the focus stays on increasing profits on what is already on the market. Numbers from the FDA however shows that the problem may not be as big as perceived, at least not now. It was shown in 2017 that about 75% of drugs

initially approved as an orphan drug have not expanded their labeled indication and that 85% of drugs approved for orphan diseases have not expanded to other conditions (Lanthier, 2017). Others again highlight that only 3 % of the approved orphan drugs truly "gamed the system" (Patel, 2017). It is still important to recognize that the drugs that seek a new indication; makes millions on it, and it is an increasing problem (K. L. Miller & Lanthier, 2018).

4.3.3 The cost of R&D and likelihood of meeting the needs

I have now shown that the pharmaceutical sector often used their R&D budget on "improving" drugs already on the market as this offers a higher return on investment. This is important to recognize since it may reduce the incentives for research on rare diseases that currently does not have a treatment. I will in this next section explore the current R&D spending.

Like any other profit maximizing company, the possibility of increased earnings is an essential reason for research and development spending in the pharmaceutical industry (S Raghavendra, Raj, Seetharaman, Rudolph Raj, & Seetharaman, 2012). EvaluatePharma (2018) has produced the graph below that shows spending (and predicted spending) on research and development from 2010 to 2024.



Graph 1: Worldwide total Pharmaceutical R&D spend in 2010-2024

We know that before the recession in 2008 there was an average spending on R&D at about 10% (S Raghavendra et al., 2012). Since recession, it declined but started going up again around 2012. We can however see from the forecast that both R&D spending is expected to

decrease in the years to come, and that the compound annual growth rate (CAGR) is expected to be lower than the years prior to 2017. The International Rare Diseases Research Consortium (IRDiRC) has a goal of 1000 new therapies in the next decade and for this goal to be reached the CAGR needs to triple (Austin et al., 2018). Based on the predictions from EvaluatePharma (2018), the tripling seems unlikely.

There are several opinions on why R&D spending's are reduced and it is not only due to repurposing of drugs. It is stated by several scholars that the pharma companies are spending less on R&D, since their revenues are decreasing as several of their blockbuster drugs are losing their patens (C. H. Song & Han, 2016).

We also know that R&D have become more expensive since each dollar spent provides a lower return on investment (ROI) than it did before due to lower success rates and more expensive trials. This is often termed the "innovation gap" (Schuhmacher, Gassmann, & Hinder, 2016). Because of this innovation gap it is estimated that the cost of developing a drug today is 2.5 times more than it was in 2003 (Graham, 2014). All of these are factors, that might lead to that the unmet need for many therapies will continue to be unmet also in the future.

5.0 DISCUSSION AND CONCLUSION

I have throughout the paper, looked at my three different research questions; *what* are the different thresholds for a rare disease around the world, *how* does one argue for the different thresholds and rarity, and *what* consequences may the thresholds lead to.

5.1 What are the thresholds

First, I looked at *what* the thresholds are in different countries and these results are presented in both table 4 and the appendix. One of the main findings in this thesis, is that the threshold for what constitutes as a rare disease differs between countries just as the rarity definition itself varies. Further I found that the normative arguments, give no clear guidance as to where the threshold should be. It has as described, been suggested by the WHO to make a universal definition, but many scholars argue against it as they believe it is too liberal and do not believe it shows "true" rarity, and this will especially be true as more and more diseases will be placed in this category due to medical interventions.

I saw that albeit it is a considerable variation on a global scale, most of the high-income countries operate with a quite equal threshold when accounting for population size and have so for years and that there is an increasing degree of convergence of the thresholds on a global scale. Another important finding is that the countries with private payers often displayed a stricter threshold than those with a third-party payer, this may be because the countries with the third-party payers often have been a contributor to R&D for orphan drugs and therefore the government feels morally obligated to provide what is available. Another reason may also be in line with my hypothesis, that these countries has a bigger focus on the welfare state, without me being able to make a strong case of it.

There seems to be a general trend that countries without an existing definition are looking to the EU and their framework as an inspiration and this is especially true for the South American countries. This inspiration is not stated in official documents, but it is highlighted in documents and news articles from interest organizations, scholars, and researchers aiming at changing policy in their own country. Some would argue that the EU may be an inspiration because they provide a quite liberal threshold compared to many countries, I especially believe this to be the reason why many interest organizations are aiming for it. A common factor for the countries without a threshold, with Canada being the main exception is that they

are on the lower end of the GDP, or they are in an economic growth phase. This was not a surprising finding, since the countries who currently have a suboptimal healthcare system may have to focus on providing and improving general care, before looking to rare diseases.

I did find that for those countries who defined a threshold based on a total population basis (an absolute threshold) such as the US and several Asian countries, the definition becomes stricter as the population is increasing. This may be a reason for changing policy in the future, as we saw became the case in Australia after much criticism from the public. The US circumvents this problem to a degree however, since they can disregard the prevalence in their orphan drug legal framework if it is no reasonable expectation for the drug to be profitable even if the disease in question is above the threshold.

5.2 How does one argue for the thresholds

This became an interesting question, as my main finding was that there is not much discussion or reasoning behind the thresholds. They seem to have been chosen quite arbitrary and this is consistent with the literature. It was initially reasoning for the one provided in the US, but as shown, this assumption of prevalence has later proved to be wrong. Still, the industry was unwilling to produce the drugs at that time, so that argument still stands. Despite the increased knowledge on prevalence in different diseases, the US has not amended their laws to reflect this. Most of the thresholds used argues that their chosen number displays a *significant* prevalence on a population level. What constitutes as significant may however, be evolving rapidly as shown, since new medical technology makes us able to define diseases more narrowly. This may lead to unforeseen consequences.

As shown, many countries look to ethics, and some uses the rule of rescue described in the theoretical framework as a reasoning when faced with public outcry. Another ethical argument often used, is that everyone should be entitled to the best possible healthcare regardless of their financial status, and this believe makes us question if it is a need for thresholds. This view is a shown not considered cost-effective and this may lead to fiscal unsustainability in the future when "everything" can be considered rare.

One potential limitation with my research, is that the countries with the most information on them are the countries with a legal framework already in place. This may be a downside since there is not much information on the arguments laid down for the threshold. In the case of the EU, a downside is that it is not possible to capture the arguments in the different countries as

the decision on a threshold was made on a supranational level. Sweden is a shown an exception here, but they too are considering changing to the EU definition.

The fact that the EU threshold is decided on supranational level is a limitation in my research since I am not able to make a strong test of my hypothesis that the countries with a higher GDP have a more liberal threshold. I do find that this is may be true since, within the same EU framework, the member states differ significantly in reimbursing based on their available budgets.

5.3 What does the thresholds lead to

The thresholds may have different implications depending on the various countries, in the Philippines for instance, you are eligible for different discounts as you are considered disabled with a rare disease. There are however implications that influences on a global scale. An important finding in the research is that the pharmaceutical companies also adapt to the rules by splitting existing diseases into smaller disease groups. This is happening on a global scale, and, it is a consequence the literature has shown was unexpected when the laws were laid down. As stated, we can now with new medical knowledge divide diseases manifold in a way that was unthinkable in 1983 when the ODA was ratified, and this opens for more drugs reaping the benefits of the current framework. The literature shows that this is not a big problem currently, but it is increasing so the incentives provided may be a future policy question.

On the other hand, although the classification and designation as an orphan drug opens for different incentives, it does not automatically equal market access or reimbursement from governmental bodies and insurance systems. A clear example of this is for instance the EU.

5.3.1 Policy questions of the thresholds

As shown in the theoretical framework, there is still not a consensus if the rarity of a disease should be considered a criterion in the case of reimbursement of drugs. The question remaining is therefore if we should value rarity in reimbursement decision when we know the orphan drugs are not cost-effective compared to some other pharmaceuticals for larger populations, and in many cases, the drugs offered are not true orphan drugs. Nor is it a general normative agreement on what should matter when deciding. Most surveys show that the

public values equality, and wishes everyone to be treated, but when faced with the notion of opportunity cost, they are more inconsistent, and this is an ethical dilemma (A. S. Desser et al., 2010).

The general public is, however, consistent when they consider severity as a criterion, and this makes us question whether they are unable to distinguish rarity and severity. Linley and Hughes (2013) showed for instance, in a survey from the UK that people favored the more severely ill regardless of the size of health gain or cost of treatment. A study from Poland also showed similar results, and it also discovered that the younger respondents are more likely than the older to favor severity when deciding on allocation (Kolasa & Lewandowski, 2015). In Norway, severity is considered a criterion when deciding on reimbursement and rarity is not (Meld. St. 34 (2015-2016), 2017) .
There also seems to be a general agreement that age should have an implicit importance when deciding on what drugs should be reimbursed and that we should prioritize the younger as this could lead to higher overall utilities because of life expectancy. This is also listed as necessary to consider but is not a criterion per se in the Norwegian national guidelines. The guidelines further states that age should not be a reason for discrimination (Meld. St. 34 (2015-2016), 2017) Rarity is not considered in reimbursement in Norway, instead it is the perceived benefit for the patient, use of resources and severity of the disease that is considered. Although rarity is not considered a criterion ,Medic et al. (2017) found in their research that it is common for European countries to reimbursed drugs for rare diseases.

Philosopher John Rawls suggested a solution for this kind of ethical dilemma by conceptualizing the Veil of ignorance. This is a concept that focuses on what choices we would take if we did not know our situation. The concept is especially applicable to healthcare as the need for medical care is often very unpredictable (Toma, Chirita, & Şarpe, 2012).

As Rawls (1971, p198) put it, "*no one knows his place in society, his class position or social status; nor does he know his fortune in the distribution of natural assets and abilities, his intelligence and strength, and the like*".

One way to use this concept in the case of policy suggestions, could be to conduct large surveys of the general public, with closed end questions. Example: would you want to reimburse a specific treatment, a question asked based on you not knowing if you were to suffer the disease or not. Kamm (2001) argues that health should be considered as a

precondition of equality of opportunity, i.e. Rawls second principle of justice. Although the thought of a Veil of ignorance is offered as a solution, or at least a way of considering the problem, it does not solve everything in practice, as resources still are scarce, independently on what the public value.

A compelling argument for why we should consider QALYs and the societal values from the EQ-5D is that it is society who are the payers. When setting the utilities through the EQ-5D, we have as a society decided behind a Veil of ignorance, how we attribute the different states, i.e. what we consider to be suffering.

Critics against the EQ-5D as the solution to the Veil of ignorance, however, claims it does not show suffering in certain diseases sufficiently as it is really an aggregation of individual valuations of those states (Whitehead & Ali, 2010). The general public for instance, often overestimates the perceived suffering of an illness (Karimi, Brazier, & Paisley, 2017). This incongruence between the perceived and experience suffering is often due to that the patients affected by a disease, are used to their condition and consider it "normal" (Gandjour, 2010). Many again highlight this overestimated perception as a positive, as it will often lead to more treatments being reimbursed, and this will benefit those suffering from a disease in the end.

Further, some countries use the ethical principle of the rule of rescue in a no small degree. This ad-hoc way of deciding may be revised in the future, as there is a rapid increase in what one considers to be a rare disease, and this method will not be economic sustainable then.

There does however seems to be a general trend with the utilitarian point of view and the notion of maximizing welfare, and the use of standardized HTAs and cost effectiveness analysis in decision making are increasing as more diseases are identified.

This increase in diseases is especially frequent when it comes to cancer, and the suggestion on raising the EU definition on rarity when looking at different types of cancers may be counterproductive in case of costs, if one were to reimburse them. Regarding the patients this would open for more treatments available; albeit dependent on reimbursement in their own country.

As I have shown throughout the paper, the incentives offered to the pharmaceutical industry is necessary for the companies to produce the drugs society needs. I have also shown some examples that the pharmaceutical industry strategically adjusts to the rules because of misaligned incentives. Therefore, the current framework may not lead to the innovation it was

set out to do. It has com apparent from the research that an increased effort investment in R&D is required for the “innovation gap”, to diminish.

These findings raise the question of whether the rules governing rare diseases achieve their intended aim and whether one might change policy to achieve the aims in a better way? One can claim that an improvement in an old drug is an innovation, but it may not be enough to meet the need for all the diseases that currently does not have appropriate treatment.

As of now, the EMA may reduce the market exclusivity by two years if a drug is considered sufficiently profitable. What constitutes this should/could be defined, since as of now this is decided on a case by case basis. Japan has as shown in their legislation, a clause that the pharma companies should pay a back tax when a drug reaches blockbuster status, and this is also suggested for the US.

Another suggestion for change in policy in the US is that the “partial” orphan drugs e.g. those already on the market when seeking new indication, should be awarded weaker benefits compared with new drugs. If this is going to be the case in the future is however questionable, and we need to tread lightly because if we reduce the incentives for orphan drugs to much, one might expect the current focus on rare diseases to diminish and this would make the patients worse of. This is also consistent with the literature, who states that as many of one third of orphan drugs would not have been developed had it not been for the incentives.

APPENDIX

Country	Threshold (Official or Unofficial)
Argentina[7]	5:10000
Australia[5]	5:10000
Brazil[8]	6,5:10000
Canada[10]	5:10000
Chile[7]	5:10000
Colombia[9]	2:10000
Denmark[10]	1-2:10000
Iceland[4]	2:10000
India[10]	1:10000
Iran[10]	2:10000
Japan[1]	4:10000
Kazakhstan[12]	1:10000
Malaysia[6]	2,5:10000
Norway[4]	1:10000
Philippines[3]	0.5:10000
Russia[4]	1:10000
Saudi Arabia[11]	5:10000
Singapore[2]	<20000
South Korea[2]	4:10000
Sweden[14]	1:10000
Switzerland[4]	5:10000
Taiwan[2]	1:10000
The EU[1]	5:10000
The US[1]	7.5:10000
Turkey[13]	1:100000

Sources: 1:(Mariz et al., 2016), 2:(P. Song et al., 2012), 3:("Rare Disease act of the Philippines REPUBLIC ACT NO. 10747," 2016), 4:(EUCERD, 2014), 5:(HealthyWa, 2019), 6: (Chu, 2019), 7: (Khosla & Valdez, 2018), 8:(Passos-Bueno, Bertola, Horovitz, de Faria Ferraz, & Brito, 2014), 9: ("Law on Policy Regulation for Rare Diseases - Law n. 1,392 of 2010 and Law n. 1,438 of 2011," 2011), 10: all thresholds provided are unofficial, and provided from the country in questions own Rare disease organization, 11:(SaudiGazette, 2017), 12:(Hedley, Murray, Rodwell, & Aymé, 2018), 13:(Akan, 2014) 14: (NNRD, 2018).

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