6-7-2025

Examining possible factors of orphan drug approval differences – A mixed-methods research

A study into factors affecting orphan drug approval time differences

Mathyn Velthuis – s3104028
GZW-2452008-4 BACHELOR THESIS
SUPERVISORS: ANNELIENE JONKER & KARIN OUDSHOORN

Table of contents

Abstract

Orphan drugs are developed to treat people living with rare diseases. Usually, these are deemed too expensive by pharmaceutical developers to develop through conventional pathways. Because of this, fewer than one-tenth of rare disease patients are able to get the treatment they need. Considering the EU estimates that around 263 to 446 million people worldwide are living with rare diseases (EU, 2025), there are still a lot of people without working treatment. Regulatory agencies that are responsible for approving new drugs within their countries are working hard to shorten the time it takes to approve new drugs. However, for developing countries there seems to be a delay in orphan drug approvals for drugs developed outside their own borders. This has severe impact on the quality of life of patients living with rare diseases and as such, it is important to know what factors are influencing orphan drug approvals worldwide.

Orphan drugs can be part of expedited programs to shorten the duration needed for approval. However, there are still differences when comparing different agencies around the world. The median approval time within expedited programs of developed countries can range from 207 to 266 days (Franco et al., 2022). For developing countries, classified as such by the United Nations Conference on Trade and Development (UNCTAD), expedited programs are either not existent or not as effective.

This research, aimed to uncover factors influencing orphan drug approvals, was done by a mixed-methods approach that includes quantitative and qualitative research. For the quantitative part novel drugs being approved between 2021 and 2024 by the United States Food and Drug Agency (FDA) were found and compared to six other agencies. For the qualitative part interviews have taken place with four individuals that have experience working in the rare disease landscape.

A total of 100 novel orphan drugs were found to be approved by the FDA between 2021 and 2024. Of these, 75 were also approved in at least one of the other included agencies. The type of drug and type of illness it was indicated for is also included and reflected upon. Of the two types of drugs, ‘Biotech’ and ‘Small molecule’, the latter had shorter approval lag time in all but one of the included agencies. The interviews that took place between May and June 2025 have resulted in eight factors that are affecting orphan drug approvals worldwide.

A summary of both the quantitative and qualitative results, combined with earlier mentioned literature, were able to answer the research question. The identified 8 factors were discussed, with recommendations given to policy makers or companies on how to shorten the time it takes to approve novel orphan drugs. Limitations of the research were that the data was acquired with the FDA as baseline, which could give out biased results, not having an included agency of a developed country bar some data on the Kingdom of Saudi-Arabia, and a small pool of interviews. Strengths of the research were the usage of a mixed-methods approach and the experience of the interviewed experts, guaranteeing credible knowledge to be passed on. Recommendations for future research would be to research approval trends over a longer period of time, and include data on the time it takes for orphan drugs to become available after HTA decisions.

1. Introduction

Orphan drugs are developed with the intention to treat rare diseases. Pharmaceutical developers worldwide experience high societal pressure to prioritize rare diseases and orphan drug development according to Vásquez et al. (2024). Developing companies need to go through certain steps to get their new drug classified as an orphan drug. Usually, this is deemed too expensive by the pharmaceutical industry to develop these drugs through the same pathway as conventional ones (Orphanet, n.d.). According to Chung et al. (2022), fewer than one-tenth of patients globally are receiving disease-specific treatment at the moment. This is because no working treatment exists yet for the other ninety percent of patients.

Rare diseases are defined differently throughout areas of the world. The European Union (EU) has defined a rare disease as one affecting less than 5 per 10.000 people. Considering that there are roughly 6000 to 8000 rare diseases classified, this means within the EU between 27 and 36 million people currently live with a rare disease (EU, 2025). The EU (2025) estimated that the global prevalence lies around 3.5 to 5.9 percent of the world's population, which corresponds to 263 to 446 million worldwide. Rare diseases do not only affect the patient, but also their family members and carers, resulting in rare diseases affecting approximately 1.05 to 1.4 billion people globally (Chung et al., 2022). While the global patient population is estimated at a low percentage of 5.9 maximum, it is urgent that all people affected by rare diseases have access to the correct medicinal treatments.

Due to the aforementioned lack of available disease-specific treatments, all layers of the global healthcare system are working hard on dedicating more time and funds into rare disease research. Regulatory agencies are responsible for approving marketing authorization for novel drugs. Both the United States Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) have shown to be effective in approving most of the novel orphan drugs over the last two decades (Downing et al., 2017). Both of these agencies have attempted to expedite drug development for serious conditions, with the FDA having four expedited programs and the EMA having three. For the FDA, these programs are called fast-track, accelerated approval, priority review, and breakthrough therapy (Michaeli et al., 2023). The EMA’s programs are accelerated assessment, conditional marketing authorisation, and the priority medicines scheme (PRIME) (Hwang et al., 2020).

When looking outside of the EU and the United States, it can be said that it can take years for orphan drugs to reach the market in most of the developing world. One example of a country where it takes a lot longer for medicines to reach the market is Japan. This country seems to experience a major delay for specifically the approval of orphan drugs developed outside of its own borders (Enya et al., 2023). This is associated by Enya et al. (2023) with smaller pharmaceutical companies in the United States not seeing enough economic gain out of exporting their developed drugs to Japan. Another country experiencing long delays for orphan drug approval is China, where it has been reported it can take nine years compared to the U.S. to get the exact same orphan drug approved (Liu et al., 2023). This is a problem affecting all patients affected by rare diseases living in these countries.

It is important to determine what directly causes these differences in drug approval worldwide within both developed as well as developing countries. Are the aforementioned expedited programs significant in speeding up orphan drug approvals for the FDA and EMA compared to other agencies? This can have significant consequences on patients living with

rare diseases as their access to orphan drugs directly impacts their quality of life. So far it is however unclear what the main factors are for this phenomenon, creating a knowledge gap. What is clear is that the difference is most evident in currently developing countries, also known as third world countries. It is important to clearly address this distinction while asking the research question:

'What are the main factors causing differences in orphan drug approval within developing countries worldwide compared to developed countries?'

This research question is split up into two sub-questions. These are as follows:

1. *'What differences in orphan drug approval times are visible when looking at orphan drugs approved between 2021 and 2024 compared to the FDA as baseline?'*
2. *'How do current programs to expedite orphan drug development influence orphan drug approvals?'*

By specifically looking for the main factors, the result of this thesis can help tackle what is the cause for orphan drug approval differences when it comes to the same drug in different countries and give advice on how to shorten the time it takes for orphan drugs to receive marketing authorizations.

2. Theory

To better understand the research question, the definition of 'drug approval' needs to be clarified. Previously mentioned research of Enya et al. (2023) and Liu et al. (2023) has defined approval as new drugs receiving marketing authorization. This decision is held as benchmark for this research, as data on marketing authorization is publicly available information given out by regulatory bodies around the world. Orphan drug approval differences are defined by the difference in days between each included regulatory body and their decision to grant the marketing authorization. Besides this, it is important to have a general understanding of the drug approval process to see where the cause of differences in approval time may lie. The differences in process between the FDA, EMA, and (some parts of) the Medicines & Healthcare products Regulatory Agency (MHRA) from the United Kingdom (UK) are compared to achieve this.

2.1 Orphan drug approval process

For both the FDA and the EMA there are five steps a new drug has to go through in the drug development process from the laboratory to ending up in the patient's hands (United States Food and Drug Administration, 2018) (European Medicines Agency, 2024). These steps are visible in Figure 1.

Steps of drug development	**FDA**	**EMA**
Step 1	Discovery and Development	Research & Development combined with Scientific advice
Step 2	Preclinical Research	Evaluation
Step 3	Clinical Research	Authorisation
Step 4	FDA Review	Access
Step 5	FDA Post-Market Safety Monitoring	Safety monitoring

Figure 1: Steps of the drug development in the FDA and EMA

Although the steps are described differently, they are roughly the same when compared. Steps 1 to 3 within the FDA are equivalent to Step 1 within the EMA with Step 4 'FDA Review' being equivalent to Step 2 and 3. Access is not mentioned in the development process of the FDA, but Step 5 is the same for both, being 'Safety monitoring' after the drug has become accessible. The focus of this thesis lies on the steps of FDA Review, Evaluation and Authorisation. In the FDA, there is a review team that looks at any New Drug Application (NDA) coming in. This team determines if the application has included all the necessary information that should be included and then has 6 to 10 months to make a decision on whether to approve the drug. This time depends on whether the drug has been handed a Priority Review designation, which is one of the four aforementioned expedited programs.

The EMA encourages developers to request pre-submission meetings about 6 to 7 months before submitting an application to ensure that a future application is compliant with all the requirements. After the developer has applied, EMA starts its assessment, asking questions to the developer and consulting additional experts in the field. Finally, the Committee for Medicinal Products for Human Use (CHMP) cast a formal vote to hand out a recommendation to approve or refuse a marketing authorisation decision. This is either done by coming to a consensus or by a majority vote within the committee. The assessment done by the CHMP takes up to 210 days, which can be reduced to 150 days if the drug was granted to be part of the accelerated assessment expedited program. Sometimes a conditional marketing authorisation based on incomplete evidence can be recommended to the European Commission if the drug is indicated for a rare disease with unmet needs. The European Commission is then to take a final decision on whether the drug will receive an EU-wide marketing authorisation (European Medicines Agency, 2024). This decision happens within 67 days of receiving the recommendation from the CHMP.

When comparing, 180 days (6 months) is the minimum amount of time for assessment by the FDA and 217 is the minimum amount of days for a drug to get approved by the EMA. This shows that between these two agencies there is already a difference in approval time. Additionally, the MHRA in the UK also has a process for orphan drugs approval. Here there is an initial assessment phase can take up to 90 days, a response assessment phase until the 150th day and finally a final assessment phase to grant application by day 210 or earlier (Government of the United Kingdom, 2025b). This is also a longer amount of time compared to the FDA, although it is possible to get approved earlier.

A study done by Franco et al. (2022) examined the median approval time of new drugs in Australia, Canada, the EU, Japan, Switzerland and the US. Here they compared expedited programs to standard pathways in the time period between 2012 and 2021. Expedited programs had median scores of approval time between 207 and 266 days. Median scores between 331 and 434 days were found for standard pathways. This shows that expedited programs are quite effective in shortening orphan drug approval. If the agencies of these developed areas already showcase differentiations in approval time, one can imagine the differences with agencies of countries that are seen as part of the developing world. To paint a picture of the regulatory landscape worldwide, Gammie et al. (2015) examined 35 countries worldwide on existing policies for orphan drugs. This was elaborated on later by Chan et al. (2020) with an even bigger sample of 200 countries and regions. It was clear that compared

with the results of Gammie et al. in 2015, major differences had occurred within this period, as lots of countries have developed new policies for improving orphan drug development. However, 108 out of the 200 countries did not have any identified orphan drug policies.

2.2 Defining developing countries

Something that now needs to be defined is the classification of developing countries. Orphan drug approval delay has a major impact on access to orphan drugs within developing countries. To be able to answer the research question, it is necessary to know what countries are generally classified as part of the developing world. Usually, a developing country is defined by its economy in comparison to the rest of the world. The United Nations Conference on Trade and Development (UNCTAD) classifies the different economies of countries worldwide and is then able to categorize them into developing or developed economies. A country then has the sovereignty to decide for themselves whether it should be classified as a developing country (UNCTAD, n.d.). An example to reflect this is South Korea, which is regarded as a developed country since 2021 (Yun-hyung, 2021). The developing economies, as classified by the UNCTAD, broadly consist of Africa, Latin America and the Caribbean; Asia with the exceptions of Japan and South Korea; and Oceania without Australia and New Zealand. In this research the focus lies on factors affecting the orphan drug approval process. These factors could be specific for developing countries or also be of note within developed countries.

2.3 Defining drug characteristics and availability

Some characteristics of drugs are worth considering when looking at drug approval times. One of these characteristics is the type of drug. The online database DrugBank distinguishes two different types: biotechnical drugs and small molecule drugs. Biotechnical drugs are biosynthesized through living cells and are regarded as structurally complex to manufacture. Small molecule drugs are made through standardized chemical processes, going through standard drug application pathways (Università degli Studi di Padova, n.d.). Another characteristic to consider is the type of disease a drug is indicated for. Kesselheim et al. (2015) found that from 1987 until 2014, most drugs designated as orphan by the FDA were indicated for oncologic or gastroenterological diseases. This could either be caused by the fact more drugs were developed for these diseases due to higher demand or could be caused by these drugs being approved faster compared to other illness types.

Finally, it is important to get a glimpse of availability of orphan drugs as a drug receiving market authorization does not mean it is immediately available. Within Europe, once the EMA has handed out marketing authorization it can take somewhere between 95 to 958 days on average for that orphan drug to become accessible for patients (Statista, 2025). Drugs being accessible is important so patients do not have to resort to medical tourism in order to receive treatment as this is not feasible for most patients (The Lancet Global Health, 2024). Medical tourism is the act of going abroad in order to get the medical treatment someone needs. During this research it is investigated if there are differences when it comes to newly approved drugs and how long it can take for them to become accessible to patients. Therefore, this research acknowledges that speeding up the process of marketing authorizations being handed to orphan drugs does not immediately solve the inequity of access to orphan drugs worldwide.

3. Methodology

To answer the research question posed earlier in the introduction, a mixed-methods approach has taken place which included both quantitative as well as qualitative research. The choice for mixed-methods was made to ensure both sub-questions were adequately answered. The first sub-question about what statistical differences are currently seen, can be answered well with quantitative research, as objective numbers can be found on which orphan drugs are approved in multiple countries. The second sub-question will have to be answered with qualitative research as it will not necessarily be objective information. Different people will hold differing opinions on what factors are either shortening or lengthening orphan drug approvals. Because of this, multiple interviews have taken place to hear from multiple experts what they think are possible factors.

As for the quantitative part of this research, a dataset was made with publicly available data about approved orphan drugs, acquired from regulatory bodies. The following steps were taken during this process:

3.1 Data acquirement

Lists of novel drugs having received approval in the United States within the years 2021 until 2024 were obtained from the regulatory body, the FDA. For each of these years there is a publicly available report showcasing all the 'New Drug Therapy Approvals', publicized on the FDA website page called 'Novel drug Approvals at FDA' (FDA, 2025). Through the nature of data acquirement originating in the FDA, the acquired data for the FDA was regarded as the standard while comparing the results. From these lists all drugs designated to treat rare or 'orphan' diseases by the FDA were collected. Specifics of each drug and whether it has been approved in other regions was then obtained from the regulatory bodies of the EU (European Medicines Agency, 2025a), the United Kingdom (Medicines & Healthcare products Regulatory Agency, 2025), the Kingdom of Saudi-Arabia (Saudi Food & Drug Authority, n.d), Australia (Therapeutic Goods Administration, 2025), Japan (Pharmaceuticals and Medical Devices Agency, 2025) and finally Canada (Government of Canada, 2019). This was done by searching for the name of the drug or its active ingredient on the websites of each regulatory body. Some of the included drugs had minor differentiations in trade names across different included regions.

3.2 Data Measuring

For all of the included regions except Saudi Arabia, the collected data included the initial marketing authorization of the drug within the region. Out of all of these countries the 'Initial Approval Date' was determined, which is equivalent to the first date that a drug was approved within the included regions. All of the included regions were then compared to the 'Initial Approval Date', resulting in a calculated variable of 'Days Since Initial Approval' for every region. This makes the approval lag that occurred visible in objective numbers. To ensure that every drug was represented correctly, the indication each drug was approved for has been included within the dataset to check whether this indication is the same in every region. This indication was linearized to a rare disease category according to the Orphanet guidelines (Orphanet, 2014). Orphanet states that it is necessary to have a monohierarchical view, also known as a linearization, available in which a disease belongs to one medical specialty or category. The linearization of a rare disease to a specialty is somewhat arbitrary as it is still up to the individual how to make use of these rules set out by Orphanet. This process was applied

here to validate the contents of the dataset. For every rare disease a definition was found in the National Library of Medicine of the USA (MedlinePlus, n.d.), after which it was determined if the disease fitted in one of the twenty-four linearization parent entities. Finally, the type of drug was collected via DrugBank (Drugbank, n.d.). This resulted in two categories: 'Biotech' and 'Small molecule'. This was needed for analyses on whether either the type of illness or the type of drug has any effect on the time it takes to approve a drug. The category 'Biotech' can also be filtered by biological groups, such as protein based therapies, gene therapies or other biologics. A full overview on these biological groups can be found in Appendix 2.

3.3 Inclusion and exclusion criteria

The drugs that have been included in this dataset where those that have been designated as orphan and have been approved by the FDA between 2021 and 2024. Prior to 2021, the withdrawal of the UK from the European Union had not been completed yet (Government of the United Kingdom, 2025a). This means that before this year, the EMA was still in charge of not only the EU, but also the UK. Since 2021, after going through a transitional period when the UK left the European Commission in 2021, the MHRA has become the standalone organisation responsible for reviewing new drug applications in the UK, and EU pharmaceutical law is no longer in effect (Criado & Bancsi, 2021). To be able to better compare the data between the MHRA and the EMA, the starting point has therefore been chosen as 2021. The cut off has been set at 2024, even though several drugs have already been approved by the FDA in 2025. This is because other regions have not yet had the time to approve these as well, and so this would skew the results.

3.4 Assessment

The search for orphan drugs resulted in a collective list that includes all of the aforementioned data. This search was conducted between March and May 2025, using either the name of the active ingredient or the name of the drug. The resources that were used to confirm that the same indication was applied were documents of product details, drug trials snapshots, summaries of product characteristics and the like.

3.5 Statistical Analysis

The collective list has been converted from an Excel file into a CSV-file, after which descriptive statistics were calculated within the program RStudio (version 2024.12.0+467). The minimum, mean and maximum duration together with the standard deviation have been calculated for days since initial approval per included region. The mean values while taking into account the type of drug or type of illness have also been calculated in this way.

3.6 Qualitative research methodology

Qualitative research intends to ask open-ended questions to explain the *how* or *why* of your research topic (Tenny et al., 2022). For the qualitative research, interviews were held with key experts on the development of orphan drugs for rare diseases. Through these interviews, it has been attempted to uncover knowledge not yet readily available through (digital) literature on factors affecting orphan drug approval times. This functions as support for the quantitative research, as just the quantitative analysis won't be sufficient to answer the research question stated earlier, due to a lack of available data on orphan drug approvals within developing countries. A grey literature search was conducted. Grey literature may include an assortment

of reports, research papers, clinical trials and other research outputs and is typically done so as to provide new information not yet published in traditional sources (Higgins et al., 2019). As a result of this interview questions have been written with the aim to answer knowledge gaps that have been found upon engaging with the literature. These questions have resulted in a fledged out interview scheme, with some differentiations specifically aimed at certain interviewees, which can be found in Appendix 3.

In total four interviews have taken place between May and June, 2025. These have been held online as the interviewees live and work within different countries and therefore also different time zones. These interviews were recorded with the consent of the interviewees, after which the recording transcript was analysed in order to make connections between the interviews and the knowledge gained from literature that the interview questions were based on. This has been done using the program Atlas.ti. Excerpts and quotes of the interviewees have been coded into groups of earlier identified possible factors that could have an influence on orphan drug approval rates worldwide.

4. Results

4.1 Quantitative results

The quantitative analysis findings consist of a total amount of 100 orphan drugs being approved by the FDA within the period of 2021 to 2024. In 2021 a total of 26 orphan drugs were approved, in 2022 a total of 20, in 2023 a total of 28 and finally in 2024 a total of 26. Out of these 100 orphan drugs 75% of them had also received a marketing authorization within at least one of the other included regions (n=75). More statistical information on specifically these 75 orphan drugs can be found in Figure 2. This leaves 25 orphan drugs that are approved by the FDA, yet are not approved by any of the other regulatory bodies. An analysis was done on these 25 drugs to determine if they are in the works to get approved. This was done by looking up if there is an active orphan designation within the other regions. The result of this analysis can be found within Appendix 4. In total 24 percent of these drugs, unapproved outside of the FDA, have received the orphan designation status from the EMA (n=6). For eight percent of these drugs there was a decision made by the manufacturer to withdraw their application to the EMA as there was insufficient data to approve the usage of the respective drug (n=2). The other 68 percent has not been found to be in the works to get approved (n=17).

DAYS APPROVED SINCE INITIAL	**USA (FDA)**	**EU (EMA)**	**UK (MHRA)**	**AUS (TGA)**	**JAPAN (PMDA)**	**CANADA (GOC)**
N(%)	75	63(84%)	59(78%)	39(52%)	23(31%)	43(57%)
MIN	0	0	0	35	0	0
MAX	3662	1217	2936	2560	1501	1414
MEAN	103	220.8	396	443	446	389.5
SD*	429.71	235.89	474.27	453.91	426.56	297.12

Figure 2: Descriptive statistics on the differences in days approved since initial approval (means rounded up to 2 decimals)*

Figure 2 gives descriptive values on the results of the 75 orphan drugs that received a marketing authorization in at least one of the included regions outside of the USA. Something that is instantly visible is the fact that for every region, bar Australia, there is a minimum value of 0 days meaning that they were the first to approve a specific orphan drug in question. This means the FDA was not the first to approve every single drug included, which was a possibility considering the data acquirement phase focused on the FDA as baseline. Below the minimum value one can see the maximum value, which stands for the longest number of days it took for each region to approve a specific orphan drug after initial approval. These values range from 1217 days in the EMA to 3662 days in the FDA. These big numbers can be explained through looking at the specific orphan drug corresponding with the maximum value. While doing so, it is noticeable that some of the included drugs were approved by the EMA before the year 2021, which is the earliest year of which the FDA has a publicly accessible list of approved new drugs. There is a drug called ‘NexoBrid’ that got approved by the EMA on the 18th of December in the year 2012. This drug was also approved by the MHRA and the FDA, except this took place in the years 2021 and 2022 respectively. For the TGA, the maximum value is a result of the drug ‘Lamzede’, which was approved by the EMA

in the year 2018. For the PMDA the maximum value is a result of the EMA approving the drug 'Besremi' in the year 2019. Lastly, Canada's maximum value is a result of the drug 'Zynlonta' being approved very recently on the 7th of march in 2025, while it was approved on the 23rd of April in 2021 by the FDA.

Next to consider are the values for mean and standard deviation for days since initial approval. The FDA has the lowest score for mean amount of days, which is a reasonable result considering the FDA is held as the standard in this research. This is showcased by the fact that only 25.33% out of the 75 drugs were initially approved outside of the USA (n=19). The standard deviation (SD) being over four times equal to the mean, shows that there is a high amount of variation for the values of the FDA. Compared to the standard set by the FDA, the EMA is the fastest with a mean value of almost 221 days and a lower SD of about 236. This showcases that there is a bit more consistency in the range of time it took to decide on marketing authorization. The MHRA and GOC have very similar mean values of 396 and almost 390 days since initial approval. They do not however have a similar value of SD, as these are scored at 474 and 297 days respectively. Finally the TGA and the PMDA have the lowest amount of the included drugs approved, while also scoring very similarly with a difference of only 3 days for their mean values and 27 days difference for the SD value.

TYPE OF DRUG	**USA (FDA)**	**EU (EMA)**	**UK (MHRA)**	**AUS (TGA)**	**JAPAN (PMDA)**	**CANADA (GOC)**
BIOTECH (N=47)*	187.98	169.43	431.79	449.57	492.71	430.71
SMALL MOLECULE (N=53)*	27.57	285.11	361.33	433.63	373.22	337.42

Figure 3: Mean values when accounting for type of drug (means rounded up to 2 decimals)*

It was taken into consideration earlier that certain characteristics of orphan drugs could possibly influence the time it takes to get approved. Figure 3 shows the mean values of days since initial approval per type of drug. The type of drug is determined by the manufacturing processes undertaken, which results in two different categories: biotechnical and small molecule. The collected data almost included an even split between the two categories, with 53 small molecule-based and 47 biotechnical orphan drugs. The 25 excluded drugs were also split very evenly with 15 small molecule-based and 10 biotechnical. With the size of this sample it is not very likely to argue that one type of drug is more likely to not get approved outside of the USA.

When looking at the mean values per type of drug it is clear that small molecule drugs are generally approved quicker than the biotechnical drugs. There is however an exception to this rule visible in the EMA, where the biotechnical drugs on average had a shorter approval lag time. For most of these regulatory bodies there is a clear margin between the two types of drugs, except for in the TGA where the difference on average is only 16 days. In the other ones the difference varies from about 70 days in the MHRA to 160 days in the FDA.

As stated earlier the indication of each drug has been collected from the included regulatory bodies and controlled to ensure that every orphan drug is approved for the same medical condition. After this, the data included 100 orphan drugs that were indicated for 83 different rare diseases. Considering this is a high number and for most diseases only one drug

has been approved, a linearization process was done with the Orphanet guidelines in mind. This resulted in 15 different prominent rare disease categories being represented, where the size of each group varied from 1 orphan drug indicated for its category to 38 orphan drugs.

A full overview of this data can be found in Appendix 5. Most categories have a very small sample of orphan drugs and consequently there are missing values here. The 3 best represented categories are most worthwhile to consider for any possible effects. These categories are the rare hematologic disease, rare neurologic disease and rare oncologic disease. For these 3 linearized groups there are respectively 10, 11 and 38 orphan drugs found within the data. In Figure 4 a total average of days since initial approval was added when combining the results on these 3 categories. The FDA is again held as the standard and had the lowest score with about 57 days average. As for the other included regions there is a variance between about 250 days to 413 days. On average Australia and Japan are the slowest, yet Japan seems to be the second fastest when it comes to orphan drugs indicated for rare neurologic diseases. They are however by far the slowest when it comes to rare hematologic diseases and only slightly slower than the other regions for rare oncologic diseases. Other highlights in the data are that EMA continues to be faster on average compared to the MHRA for every single category.

TYPE OF ILLNESS	**USA (FDA)**	**EU (EMA)**	**UK (MHRA)**	**AUS (TGA)**	**JAPAN (PMDA)**	**CANADA (GOC)**
RARE HEMATOLOGIC DISEASE (N=11)	150.18	172.11	249.71	196.8	586.6	300.4
RARE NEUROLOGIC DISEASE (N=10)	0	281.25	373.17	701	250.33	527.75
RARE ONCOLOGIC DISEASE (N=38)	21.71	295.46	337.68	340.57	384.13	365.2
TOTAL AVERAGE*	57.30	249.60	320.20	412.80	407.02	397.78

Figure 4: *Mean values when accounting for type of illness with total average score (* means rounded up to 2 decimals)*

Finally, during this research it was attempted to include the Kingdom of Saudi Arabia and possible orphan drug approval differences of this country compared to the others. However, it was unsuccessful to achieve this as the Saudi Food and Drug Authority does not have publicly available information on specific dates when drugs were approved. Twenty two percent of the 100 novel drugs approved between 2021 and 2024 by the FDA are also approved by the SFDA (n=22). To compensate for the lack of approval dates, a specific question was set up within the interview scheme, that aimed to uncover more about the orphan drug approval process done in Saudi Arabia.

4.2 Qualitative results

For this mixed-method research interviews have taken place with individuals who have experience working in the global rare disease environment. These individuals could be anyone that is affiliated with research into rare diseases and/or orphan drug approvals. Participants were recruited via professional networks, including those of the academic supervisor Anneliene Jonker, to ensure credible knowledge/relevant expertise. An overview of the interviewees can be seen in Figure 5, which includes their identities and work experience anonymized. They will be known as Individuals A to D throughout this report.

INTERVIEWEES	EXPERIENCE
INDIVIDUAL A	Experience working at RDI
INDIVIDUAL B	Experience working at EMA
INDIVIDUAL C	Experience working at PMDA
INDIVIDUAL D	Experience working at MHRA

Figure 5: Anonymized overview of the interviewees and their work experience

As previously stated, these interviews took place between the months May and June in the current year, 2025. The interview scheme consisted of 10 questions, with some of them having sub-questions to be asked when any of the interviewees answered the initial question. The average duration of these interviews was 47.25 minutes and they were all held in English. All of the interviewees were asked for their consent on being recorded for the duration of the interview. After having consented, it was once again asked during the recording whether they consent to be participating in the interview.

The transcripts of these interviews were manually coded using the program Atlas.ti, in which codes based on themes of subjects that came up in the interviews were applied to quotes from every interview. Some of these themes were pre-meditated to be included due to a specific question in the interview scheme asking about this topic. In total, this resulted in 13 different codes. A total of 112 quotes were added to one or multiple of these codes. This can be found in Appendix 6.

4.2.1 Approval times and defined timelines

First of, there is a code group called ‘Approval times’. This consists of quotes from the interviewees that describe in which way(s) the time it takes to get an orphan drug approved can be affected. Considering the research question is set up with the aim to figure out the factors that influence approval times, this is a quintessential collection of statements. One notion that all four interviewees agree on when it comes to what causes differences in the approval times of orphan drug is that it is up to the company to submit an application, and so no submission means no approval. As Individual B stated:

> “*You cannot approve a drug unless the company should meet an application. And the company, sometimes they go to the FDA and it takes them two days to [also] go to Japan. Other times it takes two years, three years or they never even go to Japan.*”

As stated in the introduction, the size of the company also was declared to be of interest by Enya et al. (2023) to explain why a company based in the USA might not start a process to get the orphan drug approved in Japan. Individual C, based in Japan, agreed on this with the following statement:

"*Big companies, they already have a branch in Japan, so that they are prepared to conduct clinical trials in Japan and submit to new drug approval in Japan. On the other hand, a small company [located] in the United States, they have no branch in Japan and no crew in Japan, so then it requires a lot of process and resources to prepare the submission in Japan, so that is a big difference. This can cause the approval differences between the United States and Japan.*"

It is ultimately down to the company to submit their marketing application to another country and if the company does not deem it economically viable for them, due to either market size or company size, their orphan drug won't be available within those other countries.

Another factor discussed in each interview was the defined timelines that are in process either in the country they find themselves working in and/or in other countries they might be knowledgeable on. Earlier in the Theory section, defined timelines were roughly discussed. As said, the FDA has defined 180 days to be the minimum amount of days for a drug to be approved. In the interview scheme, a specific question was written on the Gulf Cooperation Council Drug Regulatory (GCC-DR) agency, which overlooks collaboration between countries in the MENA (Middle-East & North-Africa) region. The GCC-DR has no defined timelines for how long it can take to get an orphan drug approved, which means it can take anywhere from 6 to 24 months (DUPHAT, 2021). This variance makes it difficult for orphan drugs to be easily accessible in the Kingdom of Saudi Arabia. However, Individual B extended the following knowledge:

"*The fact that it's been approved in another agency helps in some countries. It doesn't help in Europe. But, for example, Saudi Arabia, they tell you directly: "if your drug has been approved by the FDA or by EMA, bring it to us and we approve it straight away." Some countries do that, but they don't say it."*

It seems that in the Kingdom of Saudi Arabia a fast-tracked process of orphan drug approval is in place if a drug can be proven to be approved by the FDA or EMA. To verify this, an excerpt from the DIA Global Forum, that took place in 2019, was collected. Here it was stated that the SFDA had been working with a so-called 'Reliance Review Model' since October 2016. This model aims to work with a 60-day review procedure predicated on the approval of drugs already approved by the FDA or EMA. Next to this a 30-day review procedure is put into place when the drug is approved by both the FDA as well as the EMA (Chehimi, 2019). While this aspiration is not always achieved, the model was found to significantly reduce the average time to get orphan drugs approved down from 16-18 months (before 2016) to 6-7 months (in 2019). Chehimi stated that ever since the SFDA adopted this model, other regulatory bodies in the Middle East, such as the ones of Jordan, Egypt and the United Arab Emirates have also implemented this since 2017 and 2018 respectively.

4.2.2 Financial incentives

Another factor that aligns well with defined timelines is the existence of financial incentives. Regulatory bodies can extend financial help in multiple ways to support research activities on orphan drug development. In Japan, a few examples of financial incentives in use are subsidies granted to reduce the financial burden of product development, guidance through scientific advice for companies, preferential tax treatment and priority review (Ministry of Health, Labour and Welfare, n.d.). The interviewees were asked on the impact of such

incentives and all agreed that their effect is felt for both bigger and smaller companies. Individual A stated this on their impact:

"*That's why some of these access or fast track incentives or regulatory convergence, with the FDA and EMA for example, will be really helpful. In terms of policy that can impact drug approval times it is quite specific, it depends on the drug. In a global context I think it would stop people from applying at all, they already don't go to most countries and that is not a friendly environment*."

This tells us that, even though it can still depend on the drug as for how financial incentives can affect the approval time, they are still necessary if the global environment of orphan drug development is considered. Without financial incentives, companies would stop applying in countries where they currently do, showcased by the fact that there are still many countries where this is the case. Individual D also added on to the importance of incentives and suggests that regulatory bodies are able to join forces through joint incentives:

"*There is opportunity to try to get better alignment around the regulatory and access pathways. So the European Medicines Agency and the UK for example also offer joint scientific advice between medicines, regulators and HTA bodies and that can be a really important tool for helping to develop medicines in a way that the evidence generation fits the requirements of both medicines regulators, but also HTA and payer bodies.*"

Regulatory convergence, as how Individual A had described it, could be highly effective in this way for reducing the time it takes to get orphan drugs approved, as companies do not have to redo the process to get their orphan drug approved in a different country/region. Joint scientific advice seems to be available through the EMA with any Member State part of the Coordination Group on Health Technology Assessment (HTACG), as well as in a combination of the EMA and the FDA (European Medicines Agency, 2025b). Another example is that within the UK it is also possible to get joint scientific advice meetings set up with the MHRA and the National Institute for Health and Care Excellence (NICE) (Medicines and Healthcare products Regulatory Agency, 2025). This is the main regulatory body on making decisions for making drugs accessible in England after marketing authorization is granted by the MHRA, according to Individual D.

4.2.3 Limited resources and unmet needs

Next up, there are two factors that function in parallel to each other. Vásquez et al. (2024) stated that clinicians are more concerned with cost-effectiveness when it comes to approving and developing orphan drugs. What this means is that when there are limited resources, it is preferred to get a new drug made available for a more common rare disease. This way there is still some profit to be had as the patient population will be bigger compared to less prevalent rare diseases. This implies there is a choice to be made between either cost-effectiveness or resolving unmet needs within the orphan drug development process. This negatively impacts those patients with a less prevalent rare disease and their chances of receiving medical treatment. This is strengthened by developing countries, as classified by the UNCTAD, having limited resources, forcing them to consider what to invest in. Individual A weighed in on this with the following sentiment:

"*Here indeed they look at juggling with cost effectiveness and unmet needs but for rare diseases. When you're talking about a healthcare system, of course there are many, many*

common conditions, chronic conditions. But with rare diseases you never win with the numbers. (…) *Sometimes it is economics, but it's also the need of the population that is taken into consideration.*"

This sentiment was agreed upon by both Individuals B and D, with both saying that in any healthcare system there are always going to be resource constraints and orphan drugs for more prevalent rare diseases will always be better business for companies. One rare disease that is a bit more well-known and also more prevalent compared to other rare diseases is cystic fibrosis. There is an assortment of different medications available for cystic fibrosis (Cystic Fibrosis Foundation, n.d.), yet there are still variations of this disease that do not have any effective medication available. Within the quantitative analysis one drug called 'Alyftrek' was found to be approved by the FDA in December 2024, after which the MHRA approved it in March 2025. This specific drug aims to help cystic fibrosis patients with a certain genetic mutation, showcasing that there is still an unmet need for this patient population. Individual C responded to this news with the following statement:

"*So, I think in such situations it is similar among EU, Japan and United States because if it was a perfect drug, it can fully recover the disease so I understand there [is] no need to make other drugs, but in almost all cases the perfect drug doesn't exist. In many situations one single drug cannot recover the patient, so it is often required to get another drug or additional drugs. So it is not limited to orphan drugs but also for common diseases.*"

Unmet needs within rare diseases are of note to consider how limited resources can be spent around the world. Within developing countries it will also depend on if rare diseases can be given equal attention compared to communicable diseases or chronic diseases. In African countries communicable diseases, such as malaria, are very prevalent within the population as in 2023 the WHO African Region was home to 94% of malaria cases and 95% of malaria deaths (World Health Organization, 2024). Naturally this will be prioritized due to its prevalence, according to Individual B.

4.2.4 Prevalence definition differentiations

Earlier in the introduction it was stated that the EU defines a rare disease as one affecting less than 5 per 10.000 people. The FDA however holds a different definition of what a rare disease is, as they deem it rare when a disease has less than 200.000 patients affected. While somewhat similar, this difference might mean a drug can not be classified as an orphan drug in both Europe as well as the USA. As each country might have a different definition of the prevalence of a disease for it to be considered 'rare', this weighs heavily on countries worldwide. The aforementioned financial incentives depend on this definition to be able to give their support. Individual A also claimed this while speaking on a paper written by themselves:

"(…) *the paper is also trying to provide ground for international recognition of the same definition. This [is] so that we can also help drug development, as currently one drug can be orphan designated in one country while it isn't in a different country. Of course this is not good if we speak about incentives, as they fit in one country but not the other so that is the discrepancy. We need to have that (same definition) as it is very important and fundamental also for trials of course.*"

Meanwhile, Individual B also stated that companies have taken advantage of the differences in defined prevalence of rare diseases. By formulating the indication of their drug in such a way that it can treat a common disease, yet with enough comorbidities added for it to be less common, a company can receive benefits that are meant to be handed out to those developing orphan drugs. Individual D added on to this that it is important to consider a future where what is and what is not a rare disease is not as clear as it is now:

"*So from a prevalence perspective, many of the anatomical tumours, so pancreatic, breast or colorectal cancer, many of them are being subsetted into a lot of smaller groups. Which means that actually rare diseases is becoming a difficult term to understand in the era of personalised medicine.*"

It seems global rare disease definitions are at a threshold of changing into something else entirely and it is important for this to happen to realize more equity of orphan drug access worldwide.

4.2.5 Local policies and their effects

Besides local definitions of 'rare diseases', local policies on orphan drug development can also have a significant impact on approval differences. Two of the interviewees offered knowledge on local policies in the countries Japan and China respectively. Japan is considered part of the developed countries, while China is not (UNCTAD, n.d.). Individual C shared that in Japan there are two authorities responsible for drug development as there is the Ministry of Health, Labour and Welfare and the regulatory agency PMDA. Something of note for Japan is that a large percentage of drugs that received an orphan drug designation also got approved (Sakushima et al., 2021). Individual C explained this is due to orphan designations being given at a late stage of drug development in Japan:

"*So in the United States, in my understanding, they give orphan designations often in a very early stage of drug development. On the other hand in Japan (...), generally orphan designations are given at a late stage of drug development. So especially the clinical stage of drug development. I think in my understanding EMA is in between with a medium position. (...) The drugs in the clinical stage can relatively easily lead to the final stage of drug development and approval. Many drugs in the earlier stage cannot*."

The FDA and EMA grant an orphan designation to a drug either early on in the process or halfway, after which it goes through a marketing authorization process. In China, orphan drug development is still facing challenges compared to Japan, the USA and Europe. Individual A stated that until 2014, there was an inequity for people living in China when it came to how accessible orphan drugs were:

"(…) *for China, the provinces which are on the East Coast are [wealthier]. You know, China is massive and inland the resources are more limited. (...) What happens then is that the coverage is very limited in terms of what is reimbursed and for provinces in the coast, like Shanghai, they actually have their own additional tax. This is to set up like a dedicated rare disease fund to cover some more expensive medicines for patients. What they told us is that actually pharmaceutical companies would then go to these provinces to register and negotiate prices so that they have access to these medicines. That creates some inequity within China, of course it's a massive country, so some would have access, some others don't.*"

Before 2014, the orphan drugs patients needed weren't even available to them if they lived more inland. Individual A added that once this was changed, there was a time where less pharmaceutical companies were coming towards China to market their orphan drug, as they were able to negotiate better prices beforehand when they only came to a select amount of provinces on the coast. Li et al. (2022) published a report of an overview of China's rare disease policies and insurance system for orphan drugs. Here it is confirmed that different cities in China have their own city-wide insurance system, which means not everything is insured everywhere. In this report it is also stated that the National Medical Products Administration (NMPA) has published lists of new orphan drugs that are approved overseas and urgently need to be accessible in China as well.

Something of note here is that the World Health Organization (WHO) has compiled a list of essential medicines that should be made available in every country worldwide. They have been selected taking into account what would be the most safe and cost-effective medicines for priority conditions (World Health Organization, 2023). As the list compiled by the WHO does not include medicines necessary as treatment for rare diseases, a working group from the International Rare Diseases Research Consortium (IRDiRC) found it necessary to also compile a list of essential medicinal products for rare diseases in 2021. With this, they aimed to tackle the disparity and inequity in access for orphan drugs worldwide, stating that there has been a lot more work put into doing this for larger patient populations compared to patients living with rare diseases (Gahl et al., 2021).

The interviewees, upon asked about this essential list and whether they knew about it, were all able to speak very positively about it. They claimed it is a good idea, as it helps to visually identify what orphan drugs are out there and are deemed as a necessity to bring to all of the countries in the world. Individuals A and B emphasized the importance of including every single drug on this suggested list when trying to incorporate it, as some could 'fall through gaps'. Individual D also declared that the existence of this list does not mean that the 'problem' of rare diseases lacking treatments is fixed. This is supported by Chung et al. (2022) who estimated more than ninety percent of rare disease patients currently have not had any treatment, as also stated by Individual D. One final instance of the effects of local policies having affected orphan drug approval times is also explained by Individual D, based in the UK:

"*There are some flexibilities that the UK put in place around using the Reliance Route, which is that straight after Brexit, almost simultaneously UK could copy essentially what the EU did from CHMP opinion. So in most cases, there wasn't a big gap between those approvals provided that the company applied to the UK. I mean, there's a variety of reasons why companies may not apply to the UK, particularly in rare diseases, and that might be because of reimbursement issues or other kind of issues. So I think the data difference is most likely awaited when the UK left the EU. I assume for the drugs that are before Brexit the timelines would be pretty much the same.*"

Here it was stated that after Brexit, which is a term coined as shorthand for British exit and mentions the withdrawal of the United Kingdom from the EU (Wallenfeldt & Jeff, 2025), orphan drug approval time differences compared to the EMA began to occur. Before 2016, the UK was a member state of the EMA, which had their permanent headquarters in London until 2019 (European Medicines Agency, 2019). As such, the marketing authorization decisions for

new drugs were valid in the countries within the UK. Individual D added that for a variety of reasons the UK chose to hand out orphan designations and marketing authorizations at the same time, which is very different to EMA being able to hand out an orphan designation years before marketing authorizations. While the MHRA initially tried to replicate the EMA processes, eventually the difference in pathways lead to different approval dates of the same drug.

4.2.6 Patient involvement

Local policies are set up by regulatory bodies within each country. These can be influenced, however, by the demand of patients. Individual B talked about five different targets for patients to request an audience:

"*So they can do five things. One of them, they can just be very public: go to the media, say 'this is unfair', another thing that they do is they go and influence the funders. (...) The third one is that they are very good at raising money themselves. (...) And the [fourth] thing that they do is they influence the politicians. They go and they talk to their Member of Parliament. (...) The final one is that they try to influence the regulators.*"

Individual A recognized this as well and said that they had heard of patients speaking to ministries and agencies with the aim to get fast-tracked incentives, therefore influencing local policies. Individual C and D both agreed that patient groups are important to include in discussions, with Individual C claiming patient involvement is becoming more common in Japan. In the UK patients are increasingly embedded throughout the development programme and this seems effective, according to Individual D.

Finally, the interviewees were asked on what happens after the marketing authorization is handed out by the regulatory bodies. Earlier, Individual A spoke of citywide insurance plans affecting the accessibility of orphan drugs. They also shared an example of Côte d'Ivoire, where they had heard of chronic conditions not being covered by insurance. Medication costs for chronic conditions irrespective of rare diseases are completely on the patient. They emphasized with this example how necessary it is to get thoughtful equity-based insurance policies installed worldwide. After marketing authorization a lot still needs to happen for an orphan drug to become accessible. In the EU, the EMA grants the marketing authorization and each Member State nationally decides on making the drug accessible through HTA decisions. From then on, in most cases orphan drugs are covered by health insurance. Individual D explained that in the UK, once a new drug is available and reimbursed by the HTA body, there are no out-of-pocket costs for the patient, only a small prescription charge of £9. Within Japan, generally new drugs are covered by health insurance as well, according to Individual C. There are still challenging areas of making orphan drugs accessible, but all of the interviewees agreed that for a drug to become accessible it depends on the approval process within each country.

5. Discussion

This research was set up with the aim to get an overview of possible factors influencing orphan drug approvals worldwide. The research question to be answered was:

'What are the main factors causing differences in orphan drug approval within developing countries worldwide compared to developed countries?'.

This was split up in two sub-questions. These were as follows:

1. '*What differences in orphan drug approval times are visible when looking at orphan drugs approved between 2021 and 2024 compared to the FDA as baseline?*'
2. '*How do current programs to expedite orphan drug development influence orphan drug approvals?*'

5.1 Summary of results with comparisons to literature

A summary of the results of the quantitative research will be able to answer the first sub-question. When it came to the number of approved drugs, of the included 100, the EMA and MHRA scored the best, with 63 and 58 drugs approved respectively. Japan scored the lowest with 23 drugs approved. Looking at the type of drug, there was a clear difference between the two types of drugs. Small molecule drugs overall scored better than Biotechnical drugs when it came to approval lag time. This could be due to biotechnical drugs being regarded as more complex, therefore needing more time to be approved than the minimum amount of days set by agencies. Small molecule drugs go through standardized processes during development, which could lead to a shorter approval time due to a more streamlined experience. Looking at the type of illness characteristic, most drugs were indicated for oncological diseases, just as in the research done by Kesselheim et al. in 2015. This could be caused by there being more demand from patients with rare oncologic diseases and therefore drugs developed being approved faster, possibly even with limited evidence. Both the FDA and EMA have programs to approve drugs with limited evidence, as long as the effects of the drug are monitored frequently after reaching the market (United States Food and Drug Administration, 2018) (European Medicines Agency, 2024). It is unclear if this was the case based on the sample used for this research.

The second sub-question can be answered with the results of the qualitative results of the interviews with experts on the global rare disease landscape. Current programs to expedite orphan drug development were summed up as factors that were investigated to answer the overall research question. A particular example that was discussed is the Reliance Review Model that is used in the Kingdom of Saudi-Arabia. This program was shown to be effective in shortening the approval process for orphan drugs that were proven to be effective by other regulatory agencies. This even influenced other countries in the Middle-East to adopt this model as well. Another expedited program is the availability to receive joint scientific advice from the EMA combined with the FDA or EU Member States. There is also the possibility for the MHRA to combine with the FDA, which could shorten drug approval processes. If a developer wants to market their novel drug in both the United States and the United Kingdom or Europe, this pre-submission program could help with setting up the approval submission documents to be as complete as necessary. This might lead to regulatory agencies not finding it necessary to ask additional questions on the drug before being able to make a decision on

marketing authorization. These two discussed programs were agreed upon by the interviewees to be very effective in shortening the approval process.

The results showcased eight factors in total that were credited to cause differences in orphan drug approvals within both developed as well as developing countries. Some of these factors will be more prevalent in developing countries and vice versa. The first factor mentioned is that it is very dependent on the moment a company submits their drug for approval in a country. The size of the company was also said to play a role in this. Larger companies that already have international branches will most likely act quicker to get their drug approved in other countries. This is in line with the aforementioned literature which stated that Japan is suffering from delays when it comes to approving drugs that were developed abroad (Enya et al., 2023). Next up, the factor of defined timelines was mentioned in the theory. The interviewed experts agreed on its importance. The earlier research of Chan et al. (2020), which resulted in 108 of 200 countries not having established orphan drug policies, tells us that defined timelines are not globally in use. This could help developing countries to streamline drug approval processes. This way, a company interested in selling their drug in a new country knows what to expect in terms of response time. Another factor that was mentioned was the existence of financial incentives. Incentives will be helpful for both smaller as well as bigger companies, as developing orphan drugs is considered more costly compared to drugs for common diseases (Orphanet, n.d.). Policy makers within developing countries could consider to help companies that want to spend resources in order to market their drugs. A variety of incentives can be set in place that would make it more attractive for companies to submit their drugs in other countries.

The next factor about restricted resources also plays into this, however. The interviewed experts agreed that in any healthcare infrastructure, there is always going to be a finite amount of resources to spend. Policy makers and healthcare companies have to decide what to spend their resources on, especially in developing economies. The next factor was about cost-effectiveness or unmet needs. Pharmaceutical companies will also want to make profit off of their developed treatment, therefore Vásquez et al. (2024) stated that this makes it skewed against orphan drugs when companies develop new drugs. Possibly, it should be made more attractive for pharmaceutical developers to put time and money into medicines for rare diseases without an active treatment on the market. This could be done through more financial benefits, either tax-related or funding-related.

The next factor established was one all of the interviewees agreed on its significance. This was the effect of an established definition of rare diseases influencing orphan drug approvals. The global definition of what is seen as a ‘rare disease’ was said to be at a threshold in the results and as such, it is necessary to look at a future where this is less discernible. Variations of common diseases can result in new rare diseases and rare diseases could even grow to be seen as common diseases if they become more prevalent. In this modern era of healthcare and health technology, where it is striven to hand out personalized care, globalization of drug approval and regulatory harmonization is visible in the near future of orphan drug development. There are still a lot of countries where no orphan drug policies are in place, and as such no definitive prevalence definition is held. These countries could be lend a hand by helping them set up policies through adopting the definition held by the FDA or EMA, which are the two biggest contributors to novel orphan drug development at the moment (Downing et al., 2017). This way, it would be easier to get people from diverse

cultures with different DNA included in clinical trials and research programs around the world.

The final two factors were the impact of local policies surrounding orphan drug development and the amount of patient involvement. Some policies that were mentioned were about differentiations in the approval process. In Japan, the orphan designation is granted very late in the development process, while in the UK the designation is decided upon at the same time as the marketing authorization. It is up to the countries themselves in what way they want to organize these steps. For Japan, this system works well as 75% of medicines that were given the orphan designation were also eventually approved. This helps speed up the process of the last few steps, according to the interviewed individual based in Japan. This could be something to look into for other agencies. In the EMA, an orphan designation can be given years before a marketing authorization and this could maybe cause the process to be longer than necessary. The defined timelines that are in place within the EMA make sure that this is not the case, but for countries without defined timelines, this could be very different. Finally, when it comes to the amount of patient involvement, the demand of patients and in particular organized patient groups is felt by the pharmaceutical industry. It is important to include patients during the development of new drugs, as clinical trials include them to test novel drug developments. Their concerns over possible side-effects or the overall efficacy of the drug should be taken into account. In the results it was said patient groups are getting stronger and more organized. It is not the norm yet in all countries, however, that patient groups are engaged with orphan drug development discussions. As there is still so little known about most rare diseases, this is a challenge to overcome in the future.

5.2 Limitations & Strengths

There are some limitations and strengths to be mentioned of this research. First of all, one big limitation is the fact that within the dataset there have not been any countries included that are part of the developing countries according to UNCTAD, bar some data on the Kingdom of Saudi-Arabia. This was due to a lack of publicly available information, translated into the English language, on orphan drug approval dates. It could be that this data does exist for some developing countries within their respective regulatory bodies' archives. Another oversight in the data acquirement is that for Japan, the regulatory body PMDA has publicly shared a list of approved products, yet this list includes every approval that took place until December 2024. It could be that some of the included orphan drugs got approved in Japan since then, yet this was not available online. This information could possibly be requested from the PMDA, but the response time is estimated at 15 working days and as such, there was insufficient time to reach out to the PMDA. If the possibility of requesting this information was noticed earlier, this could have been done to ensure the data for Japan was more accurate. The final limitation on the data is that 100 drugs might be too small of a sample to draw conclusions on. The fact the data acquirement only included these specific 100 drugs based on FDA records could be changed. This research could have also been done by using the EMA as baseline while acquiring the data. Possibly, the results would have been different compared to how they look now. The EMA might have approved a different amount of novel drugs and companies developing within Europe might take shorter or longer to also market their drug within other continents. A limitation of the qualitative part of this research is that four interviews might be too low of a number to draw valid conclusions of what factors are affecting orphan drug approvals. A bigger interview sample with a more diverse background in demographics or

work experience might have led to pointing out other factors that were not included in the interview scheme.

Despite these limitations, this research possesses some strengths as well. First of all, the data that has been acquired has resulted in a new data set of more recent years. There has been other research done into orphan drug approvals per country, but not including the years 2021 to 2024 specifically. The acquiring of data in this way can be costly in time and in future research this research will help to not start out empty-handed. Another strength of this research is that the interviewees were all very experienced within the global rare disease space, with all four of them having 10-20+ years of work experience. The inclusion of these individuals will have ensured that credible knowledge was shared. The final strength of this research is in fact the use of a mixed-method approach on its own. Both methods supported each other, with insights derived from the quantitative data supporting the interview scheme and the qualitative data being able to answer the 'how' of what has influenced the orphan drug approval differences found in the quantitative data. The interviews have provided an in-depth analysis of the included perspectives where the data might not have been able to be as in-depth. The data is however very objective where the interview data is not, as it is factual information of dates when orphan drugs were approved against subjective information.

5.3 Recommendations for future research

Future research could take this research and improve upon it while looking further at how many of the included drugs become available within the included regions to decipher approval trends in the coming years. Perhaps a more in-depth look at the companies that were responsible for developing the drugs could be taken. This way it is possible to make an analysis on what type of company is more likely to submit their drug to multiple agencies. They could also possibly expand into adding HTA decisions and information on whether the drug is accessible for patients. Through this, it can be calculated how long it can take for orphan drugs to become available, just like earlier mentioned research done on the differences between European countries (Statista, 2025). Finally, it could be recommended to perform future research for a longer period of time, while periodically following the drug approval processes within regulatory bodies.

5.4 Conclusion

This research has aimed to uncover possible factors that are affecting orphan drug approval processes worldwide. This was done by a mixed-methods approach, where objective data was combined with knowledge from four experts within the rare disease landscape. The results of this research showcase orphan drug approval lag between six regulatory agencies that are part of the developed world. The data acquisition held the FDA as baseline, after which data on 100 drugs approved between 2021 and 2024 was searched for the other five agencies. Of these 100 drugs 75 percent were also found to be approved in at least one of the other agencies. This data was supported by qualitative research, where four key experts were interviewed for their knowledge on what factors could possibly influence orphan drug approvals. From this, eight different factors were identified and laid out. These factors can be used to locate where the approval process can be shortened. Possible recommendations for this were given in hopes of improving orphan drug approval processes in both developed and developing countries.

References

Chan, A. Y., Chan, V. K., Olsson, S., Fan, M., Jit, M., Gong, M., Zhang, S., Ge, M., Pathadka, S., Chung, C. C., Chung, B. H., Chui, C. S., Chan, E. W., Wong, G. H., Lum, T. Y., Wong, I. C., Ip, P., & Li, X. (2020). Access and unmet needs of orphan drugs in 194 countries and 6 areas: A global policy review with content analysis. *Value in Health*, *23*(12), 1580–1591. Retrieved February 22, 2025, from https://doi.org/10.1016/j.jval.2020.06.020

Chung, C. C. Y., Chu, A. T. W., & Chung, B. H. Y. (2022). Rare disease emerging as a global public health priority. *Frontiers in Public Health*, *10*. Retrieved February 1, 2025, from https://doi.org/10.3389/fpubh.2022.1028545

Criado, B., & Bancsi, M. (2021, May 31). *The UK regulatory landscape post Brexit*. RAPS. Retrieved June 25, 2025, from https://www.raps.org/news-and-articles/news-articles/2021/5/the-uk-regulatory-landscape-post-brexit

Cystic Fibrosis Foundation. (n.d.). *Medications*. Retrieved April 16, 2025, from https://www.cff.org/managing-cf/medications

Downing, N. S., Zhang, A. D., & Ross, J. S. (2017). Regulatory Review of New Therapeutic Agents — FDA versus EMA, 2011–2015. *New England Journal of Medicine*, *376*(14), 1386–1387. Retrieved July 2, 2025, from https://doi.org/10.1056/nejmc1700103

Drugbank. (n.d.). Browsing Drugs I Drugbank. Retrieved May 22, 2025, from https://go.drugbank.com/data_packages?utm_content=drug-card&utm_source=go.drugbank.com

European Medicines Agency. (2019, November 15). *Relocation to Amsterdam | European Medicines Agency (EMA)*. European Medicines Agency (EMA). Retrieved June 9, 2025, from https://www.ema.europa.eu/en/about-us/history-ema/relocation-amsterdam

European Medicines Agency. (2024, July 31). *From lab to patient - Timeline | European Medicines Agency (EMA)*. European Medicines Agency (EMA). Retrieved June 25, 2025, from https://www.ema.europa.eu/en/from-lab-to-patient-timeline#read-more

European Medicines Agency. (2025a, May 22). *Search | European Medicines Agency (EMA)*. European Medicines Agency (EMA). Retrieved May 22, 2025, from https://www.ema.europa.eu/en/search

European Medicines Agency. (2025b, January 22). *Parallel scientific advice and special development aspects or product types | European Medicines Agency (EMA)*. European Medicines Agency (EMA). Retrieved June 9, 2025, from https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance/parallel-scientific-advice-special-development-aspects-or-product-types

Enya, K., Lim, Y., Sengoku, S., & Kodama, K. (2023). Increasing orphan drug loss in Japan: Trends and R&D strategy for rare diseases. *Drug Discovery Today*, 28(10), 103755. Retrieved February 22, 2025, from https://doi.org/10.1016/j.drudis.2023.103755

European Union. (2025, February 24). *Rare diseases*. Public Health. Retrieved February 28, 2025, from https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/rare-diseases_en

FDA. (2025, February 6). *Novel drug approvals at FDA*. U.S. Food And Drug Administration. Retrieved April 2, 2025, from https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda

Franco, P., Jain, R., Rosenkrands-Lange, E., Hey, C., & Koban, M. U. (2022). Regulatory pathways supporting expedited drug development and approval in ICH member countries. *Therapeutic Innovation & Regulatory Science*, *57*(3), 484–514. Retrieved July 2, from https://doi.org/10.1007/s43441-022-00480-3

Gahl, W. A., Wong-Rieger, D., Hivert, V., Yang, R., Zanello, G., & Groft, S. (2021). Essential list of medicinal products for rare diseases: recommendations from the IRDiRC Rare Disease Treatment Access Working Group. *Orphanet Journal of Rare Diseases*, 16(1). Retrieved February 11, 2025, from https://doi.org/10.1186/s13023-021-01923-0

Gammie, T., Lu, C. Y., & Babar, Z. U. (2015). Access to Orphan Drugs: A comprehensive review of legislations, regulations and policies in 35 countries. *PLoS ONE*, 10(10), e0140002. Retrieved February 21, 2025, from https://doi.org/10.1371/journal.pone.0140002

Government of Canada. (2019, March 1). *Search criteria - Drug Product Database online query*. Government of Canada. Retrieved May 12, 2025, from https://health-products.canada.ca/dpd-bdpp/

Government of the United Kingdom. (2025a, March 11). *Orphan medicinal products*. GOV.UK. Retrieved June 25, 2025, from https://www.gov.uk/guidance/orphan-medicinal-products-in-great-britain

Government of the United Kingdom. (2025b, May 22). *National assessment procedure for medicines*. GOV.UK. Retrieved June 25, 2025, from https://www.gov.uk/guidance/national-assessment-procedure-for-medicines

Higgins, J., Thomas, J., & Chandler, J. (2019). *Chapter 4: Searching for and selecting studies*. Cochrane Training. Retrieved June 4, 2025, from https://training.cochrane.org/handbook/current/chapter-04#section-4-3-5

Hwang, T. J., Ross, J. S., Vokinger, K. N., & Kesselheim, A. S. (2020). Association between FDA and EMA expedited approval programs and therapeutic value of new medicines: retrospective cohort study. BMJ, m3434. Retrieved July 2, from https://doi.org/10.1136/bmj.m3434

Kesselheim, A. S., Wang, B., Franklin, J. M., & Darrow, J. J. (2015). Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. *BMJ*, h4633. Retrieved July 2, from https://doi.org/10.1136/bmj.h4633

Li, Y., Parexel Regulatory and Access Consulting, Cheng, G., Health Advances, Woo, E., Health Advances, Guo, J., Illness Challenge Foundation, & Parexel International Corporation. (2022). *An overview of China's market approval policy and medical insurance payment system for rare disease drugs*. Retrieved May 12, from

https://www.parexel.com/application/files/resources/assets/overview-of-chinas-market-approval-policy-med-insurance-payment-system.pdf

Liu, J., Yu, Y., Zhong, M., Ma, C., & Shao, R. (2023). Long way to go: Progress of orphan drug accessibility in China from 2017 to 2022. *Frontiers in Pharmacology*, 14. Retrieved February 26, 2025, from https://doi.org/10.3389/fphar.2023.1138996

Medicines & Healthcare products Regulatory Agency. (n.d.). *MHRA Products | Search results*. Retrieved May 12, 2025, from https://products.mhra.gov.uk/search/?search=skytrofa&page=1

MedlinePlus. (n.d.). *MedlinePlus - Health Information from the National Library of Medicine*. Retrieved May 20, 2025, from https://medlineplus.gov/

Michaeli, D. T., Michaeli, T., Albers, S., Boch, T., & Michaeli, J. C. (2023). Special FDA designations for drug development: orphan, fast track, accelerated approval, priority review, and breakthrough therapy. *The European Journal of Health Economics*, *25*(6), 979–997. Retrieved March 4, 2025, from https://doi.org/10.1007/s10198-023-01639-x

Ministry of Health, Labour and Welfare. (n.d.). *Overview of Orphan Drug/Medical Device Designation System*. Retrieved April 16, 2025, from https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html

Orphanet. (2014). *Orphanet linearisation rules for rare diseases - Procedural Document*. Retrieved May 22, 2025, from https://www.orphadata.com/docs/Orphanet_linearisation_rules.pdf

Orphanet. (n.d.). About orphan drugs. Retrieved March 2, 2025, from https://www.orpha.net/en/other-information/about-orphan-drugs?stapage=what

Pharmaceuticals and Medical Devices Agency. (n.d.). List of approved drugs. In *Review Category Products*. Retrieved May 12, 2025, from https://www.pmda.go.jp/files/000274881.pdf

Sakushima, K., Takeda, H., & Aoi, Y. (2021). Orphan drug designation and development in Japan: 25 years of experience and assessment. *Nature Reviews Drug Discovery*, *20*(12), 893–894. Retrieved May 13, 2025, from https://doi.org/10.1038/d41573-021-00045-3

Saudi Food & Drug Authority. (n.d.). *Drugs list | Saudi Food and Drug Authority*. Retrieved May 12, 2025, from https://www.sfda.gov.sa/en/drugs-list

Statista. (2025, January 13). *Time between orphan drugs approval and patient access in Europe 2024, by country*. Retrieved March 3, 2025, from https://www.statista.com/statistics/1248711/europe-time-between-orphan-drugs-authorization-and-access/

Tenny, S., Brannan, J. M., & Brannan, G. D. (2022). Qualitative study. In *StatPearls*. StatPearls Publishing. Retrieved March 9, 2025, from https://www.ncbi.nlm.nih.gov/books/NBK470395/

The Lancet Global Health. (2024). The landscape for rare diseases in 2024. *The Lancet Global Health*, *12*(3), e341. Retrieved February 1, 2025, from https://doi.org/10.1016/S2214-109X(24)00056-1

Therapeutic Goods Administration. (2025, March 4). *Australian Register of Therapeutic Goods (ARTG)*. Therapeutic Goods Administration (TGA). Retrieved May 12, 2025, from https://www.tga.gov.au/resources/artg

United Nations Conference on Trade and Development. (n.d.). *Classifications | UNCTAD Data Hub*. United Nations. Retrieved March 4, 2025, from https://unctadstat.unctad.org/EN/Classifications.html

Università degli Studi di Padova. (n.d.). *What is the difference between biotechnological drugs and traditional drugs?* Future Learn. Retrieved June 2, 2025, from https://www.futurelearn.com/info/courses/getting-to-know-pharmaceutical-biotechnologies-more-than-science-in-a-lab/0/steps/406214#:~:text=small%20molecule%20drugs%20are%20typically%20synthesized%20through%20standardized%20chemical%20processes%20resulting%20in%20well%2Ddefined%20structures

Vásquez, P., Hall, L., & Merlo, G. (2024). Societal Preferences in Health Technology Assessments for Rare Diseases and Orphan Drugs: A Systematic Literature Review of New analytic Approaches. *Value in Health Regional Issues*, *44*, 101026. Retrieved February 28, 2025, from https://doi.org/10.1016/j.vhri.2024.101026

Wallenfeldt, & Jeff. (2025, June 9). *Brexit | Meaning, Referendum, date, & Consequences*. Encyclopedia Britannica. Retrieved June 9, 2025, from https://www.britannica.com/topic/Brexit

World Health Organization. (2023, July 26). WHO Model List of Essential Medicines - 23rd list, 2023. Retrieved February 10, 2025, from https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

World Health Organization. (2024, December 11). *Malaria*. Retrieved June 9, 2025, from https://www.who.int/news-room/fact-sheets/detail/malaria#:~:text=The%20WHO%20African%20Region%20carries,malaria%20deaths%20in%20the%20Region.

Yun-hyung, G. (2021, May 7). UNCTAD classifies S. Korea as developed economy. Hankyoreh. Retrieved March 5, 2025, from https://english.hani.co.kr/arti/english_edition/e_international/1002230.html

Appendix 1: AI Statement

During the preparation of this work, I used no artificial intelligence tools and take full responsibility for the final outcome.

Appendix 2: Biologic groups of the 'Biotech' category

Groups	**Sub-categories with the number of each found**	**Total amount**
Protein Based Therapies	Bispecific monoclonal antibody (n=2), Fusion proteins (n=1), Hormones (n=2), Interferons (n=1), Monoclonal antibody (mAb) (n=21), Peptides (n=3), Recombinant Enzymes (n=3) and Other protein based therapies (n=4).	37 total
Gene Therapies	Antisense Oligonucleotides (n=6).	6 total
Other Biologics	None specified	4 total

Appendix 3: Interview scheme

Introduction	Hello and good morning/afternoon/evening. Thank you for taking the time to participate in this interview. My name is Mathyn Velthuis and this interview is part of my bachelor thesis research on the worldwide impact of rare diseases. More specifically, my research is about orphan drugs and the duration that is needed for approval across countries and possible differentiations found between them. Access towards orphan drugs is impacted by different factors worldwide and through doing this research my aim is to identify these factors as accurately as possible. This is done partly through researching available data on orphan drug approvals within different parts of the world and partly through interviewing research experts on the rare disease landscape worldwide. During this interview, try to formulate your answers as specific as you can. If a question isn't clear please feel free to share this so I can possibly try to explain the background context of the question. Some questions will already have a short explanation beforehand to introduce a new topic. If you personally don't know the answer to a question, please also share this so we can move to a next question. At any point during this interview, you are allowed to retract your participation and stop the interview. Would you be open to me making an audio recording of this interview, through Microsoft Teams/Zoom (application currently in use)? This recording will be encrypted and stored throughout the duration of my research and will afterwards be permanently deleted. If you consent to this, I will now start this audio recording. The answers given out by you will be encrypted, ensuring you will remain fully anonymous within this research. I have received an ethical approval under the supervision of dr. Anneliene Jonker. Before we start, may I formally ask for you to give your consent to be interviewed for this researched? Now, I will start with the interview questions.
Background question	Can you tell me something about your occupation, the organization you work for, the activities your work entails and how long you have been working within the rare disease landscape?
Topic list	*Orphan drug development process*

	As a start, I am curious on your knowledge on centralized collaboration & centralized drug approval review processes. For orphan drugs it is compulsory to sign into joint collaboration processes within Europe through the EMA. • What are possible barriers and stimulants to centralized cooperation between agencies within different regions or countries? o What are possible advantages of performing the orphan drug research only within a singular country? Does this result in a medicine being available faster? o What elements of this process are easier done while cooperating with other regions and what elements in turn become more difficult and how does this influence drug approval times? Collaboration between countries is done through the Gulf Cooperation Council in the MENA region (Middle-East & North Africa). One current aspect of this collaboration is that they do not work with defined timelines for drug registration approval, which means the review process can take from 6 to 24+ months. • Can you think of any possible opportunities and barriers towards implementing defined timelines for orphan drug approval in these countries? o Adding on to this, in many countries there already exist strict defined timelines for orphan drug approval. How do these influence the process and has this shown to decrease the time it takes to approve orphan drugs? Sometimes new drugs are approved for a rare disease that already has existing drugs on the market, this has to do with helping patients with a genetic variation of the same illness also get the medical help they need as the existing drugs don't hold any effect for them. This comes down to choosing between targeting unmet needs or cost-effectiveness when approving new drugs. • Can you tell me something about the thought process behind choosing for approving drugs that will provide patients with unmet needs or drugs that have the best market potential? o If so, could you come up with possible reasoning behind both opinions? • Have you ever worked together with a patient group in your occupation? If so, in what way? *Local policies* Next I would like to ask some questions about local policies as a possible contributing factor on orphan drug approval times. I have a short background story about South Korea to start off. Nowadays South Korea is seen as part of the developed world since 2021, but back in 2016 the country had only just launched its 'Rare Disease Management Act'. However in the years 2018 and 2019 the NDA (new drug approval) review times were actually longer for orphan drugs compared to conventional drugs. According to Choi et al. (2022) this could have been caused by a revision of the Pharmaceutical Affairs act in 2014, resulting in orphan drugs losing a exemption of GMP inspection, thus the review period gradually increased. • What are the most effective local policies you can think of that have a significant impact on drug approval times? o Can you think of any local policy changes that have been proven to be effective for improving orphan drug approval times? Either within your own country or a country you hold more knowledge on? • Is it common for exemptions for orphan drugs to be removed like in this example? o If so, can you possibly elaborate on what impacts these decisions and how this affects ongoing approval processes? For a resource map done by Rare Diseases International (RDI) on the rare disease landscape in Africa and the Middle-East a few things are considered. One of them is whether a country prioritizes rare diseases over other diseases such as communicable diseases. It is also taken into account whether the country has a definition and prevalence recorded within its policies. • Does a priority towards rare diseases get influenced by the prevalence of communicable diseases compared to them?

	○ Is a choice to prioritize either of these influenced by the available resources a country has? Think of the amount of researchers or money that is available to spend on research and what a country wants to gain out of this. • There are lots of different defined prevalences within different countries. Does this influence whether a new drug gets the possibility to be designated as an orphan drug within that country? The WHO has compiled a list of worldwide essential medicines. In 2021 an IRDiRC working group established a suggested essential list of orphan drugs. They did this with the aim to tackle disparity and inequity in access for orphan drugs worldwide (Gahl et al., 2021). • What are opportunities and barriers for making use of this list worldwide? *Financial factors on orphan drug access* A country can decide to offer financial incentives through their national ministry of health. In Japan the Ministry of Health, Labour and Welfare offers subsidies, preferential tax treatment, priority review among other incentives. • From my statistical research for my thesis I have compared orphan drugs approved from 2021 onward within a few countries with the USA's FDA as base point. I noticed that Japan compared to the FDA is sometimes very quick at approving the same drug, sometimes even earlier, but other times it took between 200 and 1000 days to approve the same drug. What are possible reasons for this discrepancy? • What kind of effects do different financial incentives have on orphan drug approval times? ○ What incentives are in use within your country and do they work together with the active local policies? ○ Have these incentives made a difference in decreasing the time needed for orphan drug approval? ○ If yes, can you elaborate on how this could possibly be implemented more worldwide? Could organisations across continents perhaps cooperate? • Finally, health insurance policies can influence whether an orphan drug once approved is available for the public. What can you tell me about the impact of free versus fixed pricing based on your expertise? ○ Does free or fixed pricing occur more often for orphan drugs?
Summarizing and final question	We have reached the end of the questions for this interview. Did I miss anything that wasn't mentioned that you think is important to keep in mind?
Closing	This is officially the ending of the interview. Once again I want to thank you very much for participating in this. If there's anything you can think of afterwards that wasn't mentioned, I hope we can stay in contact. Would you be interested in me sending the transcript of this interview and/or the finished product of my thesis assignment once this research has concluded? One final time I thank you for your participation and I wish you a good day!

Appendix 4: Data on 25 orphan drugs only approved by the FDA

Drug name	Type of drug	Date approved	Indication	Licensed company	Orphan designation	Other notable info on pipeline
Amondys 45	Biotech	25-2-2021	Duchenne muscular dystrophy	Sarepta Therapeutics	No	
Cytalux	Small molecule	29-11-2021	ovarian cancer lesions	On Target Laboratories, LLC	No	

Exkivity	Small molecule	15-9-2021	locally advanced or metastatic non-small cell lung cancer	Takeda Pharma	No	Withdrawal of application in EMA on 20-7-2022
fexinidazole	Small molecule	16-7-2021	human African trypanosomiasis caused by the parasite Trypanosoma brucei gambiense	Sanofi-Aventis	No	Positive opinion by EMA for use in non-European markets in 2018
Truseltiq	Small molecule	28-5-2021	cholangiocarcinoma	QED Therapeutics	No	FDA announced withdrawal of approval on 16-5-2024
Ukoniq	Small molecule	5-2-2021	marginal zone lymphoma and follicular lymphoma	TG Therapeutics	No	FDA announced withdrawal of approval on 1-6-2022
Relyvrio	Small molecule	29-9-2022	amyotrophic lateral sclerosis	Amylyx Pharmaceuticals	No	Amylyx announced withdrawal from the market in the US and Canada on 4-4-2024
Rezlidhia	Small molecule	1-12-2022	relapsed or refractory acute myeloid leukemia	Rigel Pharmaceuticals	Yes	Orphan designation in EMA on 29-5-2019
Terlivaz	Biotech	14-9-2022	hepatorenal syndrome	Mallinckrodt	No	Active substance deemed too high risk by the EMA
Vonjo	Small molecule	28-2-2022	intermediate or high-risk myelofibrosis in adults with low patelets	CTI BioPharma (Sobi)	Yes	Orphan designation in EMA on 25-8-2010
Aphexda	Biotech	8-9-2023	mobilize hematopoietic stem cells in patients with	BioLineRX	No	

			multiple myeloma			
Ogsiveo	Small molecule	27-11-2023	progressing desmoid tumors	Springworks Therapeutics	Yes	Orphan designation in EMA on 17-10-2019, marketing authorization application on 29-2-2024
Rivfloza	Biotech	29-9-2023	primary hyperoxaluria type 1	Dicerna Pharmaceuticals (Novo Nordisk)	No	
Veopoz	Biotech	18-8-2023	CD55-deficient protein-losing enteropathy	Regeneron Pharmaceuticals	No	
Aqneursa	Small molecule	24-9-2024	Niemann-Pick disease type C	IntraBio	No	
Bizengri	Biotech	4-12-2024	non-small cell lung cancer and pancreatic adenocarcinoma	Merus	No	
Crenessity	Small molecule	13-12-2024	classic congenital adrenal hyperplasia	Neurocrine Biosciences	No	
Imdelltra	Biotech	16-5-2024	extensive stage small cell lung cancer	Amgen	Yes	Orphan designation in EMA on 12-1-2024
Miplyffa	Small molecule	20-9-2024	Niemann-Pick disease type C	Zevra Therapeutics	No	Withdrawal of application in EMA on 22-3-2022
Niktimvo	Biotech	14-8-2024	chronic graft-versus-host disease	Incyte	No	
Ojemda	Small molecule	23-4-2024	relapsed or refractory pediatric low-grade glioma	Day One	No	
Revuforj	Small molecule	15-11-2024	relapsed or refractory acute leukemia	Syndax	No	

Tryngolza	Biotech	19-12-2024	familial chylomicronemia syndrome	Ionis Pharmaceuticals	No	
Xolremdi	Small molecule	26-4-2024	WHIM syndrome	X4 Pharmaceuticals	Yes	Marketing authorization application in EMA on 24-1-2025
Ziihera	Biotech	20-11-2024	unresectable or metastatic HER2-positive biliary tract cancer	Jazz Pharmaceuticals	Yes	Positive opinion by EMA for conditional marketing authorisation on 25-4-2025

Appendix 5: Mean values when accounting for type of illness

TYPE OF ILLNESS	USA (FDA)	EU (EMA)	UK (MHRA)	AUS (TGA)	JAPAN (PMDA)	CANADA (GOC)
INBORN ERRORS OF METABOLISM (N=7)*	293.86	188.67	782.5	1510	NA	NA
RARE BONE DISEASE (N=1)	573	NA	NA	NA	NA	0
RARE CIRCULATORY SYSTEM DISEASE (N=4)	2.5	240.75	317.67	287.33	68	182.67
RARE DEVELOPMENTAL DEFECT DURING EMBRYOGENESIS (N=3)	0	49	175	NA	NA	NA
RARE ENDOCRINE DISEASE (N=3)*	231.33	83.33	284	174.5	298	0
RARE GASTROENTERELOGIC DSEASE (N=3)	64	149.33	332.33	401.5	561.5	602.33
RARE HEMATOLOGIC DISEASE (N=11)*	150.18	172.11	249.71	196.8	586.6	300.4
RARE HEPATIC DISEASE (N=2)	34	0	38	426	NA	614
RARE IMMUNE DISEASE (N=6)	0	264	362.5	506.5	NA	319
RARE INFECTIOUS DISEASE (N=3)	4.67	137.5	340	332	958	310
RARE NEUROLOGIC DISEASE (N=10)*	0	281.25	373.17	701	250.33	527.75
RARE ODONTOLOGIC DISEASE (N=2)	0	NA	356	119	984	250

RARE ONCOLOGIC DISEASE (N=38)*	21.71	295.46	337.68	340.57	384.13	365.2
RARE SKIN DISEASE (N=5)	842.2	107	887.2	899	NA	566
RARE UROGENITAL DISEASE (N=2)	0	NA	NA	NA	NA	NA

Appendix 6: Coding overview in Atlas.ti & collection of used quotes

Main category	Code group	Code name	Contents of quote	Interviewee
Orphan drug approval lag factors	Accessibility	Availability of orphan drugs	You don't pay for drugs in Europe and are then reimbursed. That is the case in America, in Europe we have National Health systems.	Individual B
			The government will decide what they pay for or not.	
			Even if you have the EMA their centralised approval, different European countries then have to approve it.	Individual A
			In Zimbabwe, importing medicines was done through a middle person, but not anymore.	
			Fast track incentives, with the FDA and EMA for example, will be really helpful.	
			Access is such a challenge for many countries, there is no submission, no approval.	
			In countries outside Africa and MENA, there has always been competition with non-communicable diseases aswell.	
			If you have good insurance, then you might have access to orphan drugs.	
			In most countries insurance works with universal health coverage, which rare diseases are part of.	
			For d'ivoire coast, we were told chronic conditions are not covered at all.	
			The final objective is for patients to have these medicines and steps should be	

			taken to address the global need.	
			There are still opportunities for older medicines for rare diseases in terms of global accessibility.	
			Generally new drugs are covered by health insurance, so they are covered even if it's very expensive.	Individual C
			If it is reimbursed by the HTA body, you don't pay anything in our health system.	Individual D
			Once marketing authorization is granted, the drug goes through HTA bodies before patients get access.	
			For a relatively small company filing in Japan, where you will need Japanese resources for, is definitely an added barrier.	
			Sometimes these medicines for rare diseases are some of the more costly medicines being considered by HTA bodies.	
			In the UK you pay a small prescription charge, which is about 9 pounds for some of the smaller medicines.	
			In a future horizon scanning view there is an opportunity to see where the rare disease field is going to be compared to now.	
	Patient impact	Patient groups	Patient groups exist, and are getting stronger.	Individual B
			More and more patient statements and involvement is included in HTA assessments.	Individual A
			We have heard of patients trying to get a fast-track process set up in their country.	
			In Ghana there are access programmes and in Brazil there are regulations on clinical trials for rare diseases, involving patient groups.	

			In my experience, patient engagement is becoming more common in Japan, like in the EU.	Individual C
			Patient groups often visit the health ministry MHRW in Japan.	
			Discussions on implementation involved patients as they were embedded throughout the development programme.	Individual D
			There are a number of tools to support patients, resulting in patients being increasingly involved in decision making.	
		Societal pressure	Patient groups can put their pressure towards five groups of people.	Individual B
			A few years ago a medicine for ALS was approved by the FDA due to pressure, but it was not found effective.	
			There is no evidence that it works but there is pressure to approve it, however a drug without evidence is super dangerous.	
			The priority is changing because of pressure depending on what is more common within a country, rare or common diseases.	
			For countries with a higher prevalence of maria for example, this is prioritized as it is what the population needs more.	
			A condition being rare does not mean that it is not important, the need of the population is taken into consideration.	Individual A
	Policies and medicines	Effects of local policies	It takes a long time for changing policy to have effects, more than two or three years.	Individual B
			The fact a drug is approved by other agencies helps in some countries.	

		Sometimes agencies make different decisions for the same drug, while the evidence is the same.	
		Companies need to bring their drug over to other countries and they currently do not, because it is a lot of work.	
		In Africa and MENA there is a lot of competition for attention towards rare diseases with communicable diseases as they are more prioritized.	Individual A
		In China, cities on the coast are wealthier and used to have better access to orphan drugs.	
		Since 2014, there is more equity in access to orphan drugs in China.	
		PMDA and MHLW work together to develop and approve drugs in Japan.	Individual C
		Orphan designation cannot be removed in Japan during the review process of new drug approvals.	
		Orphan designation is handed out at a late stage of drug development, which makes the drugs easier to get approved.	
		Following Brexit, the UK chose to hand out orphan designation and marketing authorization at the same time.	Individual D
		The UK has only been out of the EU for maybe five or six years, so I think our system is still stabilising.	
		Countries in the UK have national plans on rare diseases that include recommendations around access to medicines.	
		Straight after Brexit, the UK could copy what the EU decided using a Reliance Route.	

		There is a market exclusivity period of 10 years in the UK, this can be different in other countries.	
	Essential medicines	I think it is a very good idea to have this essential medicines list.	Individual B
		The list brings transparency on decision making, as countries can take the recommended list from IRDiRC and explain why some drugs are approved.	
		You have to keep in mind that every drug on the list has to be included.	
		The model list for common drugs is prepared by the WHO and is reviewed every two years.	Individual A
		Having this list is already a good step in identifying what are the most important medicines for rare diseases.	
		In Canada, they looked at this list and were able to benchmark what is actually available, I think it was only 60 percent.	
		We found that there are many gaps in the global model list, it needs to be strengthened so that every drug is available.	
		Pharmaceutical companies need to be suggested to consider the whole drug cycle: what happens after patent expiry?	
		I only know of the existence of the list of IRDiRC, but do not know much about the contents and the development of it.	Individual C
		I think having a list is really helpful as it raises the visibility of what therapies are available for rare diseases.	Individual D
		The danger is that it may look like the problem of rare diseases is solved, but there	

			are still 95 percent of rare disease patients without any therapies available.	
		European policy	In Europe, every country has agency but the marketing authorization can only be given by EMA.	Individual B
			If you only want to market in one country in Europe, you still have to go through EMA.	
			The marketing authorization applicant puts the request to EMA, where a committee of 50 people is taking the decision if the drug is going to be approved or not.	
			The final decision is with a vote and you need to have a majority.	
			Sometimes when a drug has priority, you go faster. But if the drug is very complicated, it does not normally work like that.	
			If you come to Europe saying that your drug is approved by the FDA, it does not help. All the evidence needs to be brought to EMA as well.	
			A lot of the decisions of FDA and EMA are overlapping but there are a few when given the same evidence that differ.	
			The speed depends on the type of drug with fast-track processes.	
			It is very beneficial to have such joint collaboration processes in Europe as maybe not all countries are able to review such documentation.	Individual A
			I am not familiar with other regions that have regulatory harmonisation and convergence such as the EMA.	
			At the EMA, it is an advantage for companies that applying for marketing authorization grants you	Individual D

			market opportunities in the 27 member states.	
			When you want to launch your drug in multiple countries, it is quite a burdensome process overall.	
			Before Brexit, the UK used to follow the rules of the EMA where orphan designation is handed at any point before the marketing authorization.	
			In Europe at least you now have the joint clinical assessment with the new regulation on HTAs.	
	Prevalency differences	Differences in defined prevalence	Normally the rare disease prevalence is defined in how many people have the disease, like 5 per 10.000 in Europe.	Individual B
			Companies are very sneaky, they can define the indication in a way that orphan designation is granted for more common diseases.	
			Remember also that the orphan definition is not the same in Europe as America.	
			Historically rare diseases have been starting to get defined since the FDA launched the Orphan Drug Act in 1983, after which other countries came along.	Individual A
			We need to have that same definition as it is very important and fundamental for incentives and clinical trials.	
			Rare diseases is becoming a difficult term to understand in the era of personalised medicine.	Individual D
			Not only in oncology but also other disease areas are going to become increasingly personalised so defining rare is a topic that has to be addressed rather quickly.	
			The FDA is much more permissive with accepting	

		approaches from a subsetting process than the EU is.	
		Some rare diseases are going to be common enough to go through a normal development programme but for a large subset of rare diseases that is not going to be the case.	
Resources and unmet needs	Allocating available resources	There is no right or wrong, each country will decide what to do but only up to a point.	Individual B
		It makes sense to put your resources in something that is doing a lot of damage to your country e.g. malaria killing thousands in Africa.	
		Until 20 to 30 years ago orphan diseases were less important, as cardiovascular and oncological diseases were more prevalent.	
		Clinical trials for different agencies produce nearly the same evidence.	
		In Norway, they do not believe in orphan drugs as they say it is not fair to give more money to diseases due to rarity.	
		Larger companies will be the ones going to more agencies than smaller companies.	
		Communicable diseases are priority in Africa and MENA.	Individual A
		A barrier is that it is quite a burdensome process for approvals.	Individual D
		In any health system and infrastructure there is always going to be resource constraints.	
		A relatively small company has a hard time filing in Japan.	
	Cost-effectiveness versus unmet need	If you are a developer, you want to make profit with your medicine.	Individual B

			Rare diseases that are a bit more common than ultra rare diseases will always be better business.	
			Injections are painful and visits to the doctor are not free so approving drugs without good evidence is not a good idea.	
			You start with an orphan drug that hopefully will later be able to get converted into a generic drug.	
			Financial incentives do help but more for the less expensive drugs to make, advanced therapies are hard to make and expensive.	
			It is always down to the science and efficacy, if you can safely demonstrate this the HTA will decide on covering the medicine with insurance.	Individual A
			The WHO are juggling with cost-effectiveness and unmet needs when it comes to setting up model lists of essential medicines.	
			If there was a perfect drug it can fully recover the disease, so I understand there is need to make more drugs for the same rare disease.	Individual C
			There are parts of the regulatory system to support rare diseases partly because of the higher medical needs of most of these patients.	Individual D
			I think there is opportunity to recognise the challenges of developing medicines in small populations.	
	General opinions on factors involving approval times	Approval times	There are several very important factors on the difference in approval times.	Individual B

			The first factor is that you cannot approve a drug unless the company sends out the application and it can take from two days to three years.	
			From the orphan drugs approved in 2002 and 2003 80% of them are in either EMA or the FDA, but very few are in other countries.	
			Rather than having companies going country by country to file for approval, centralized processes speed up the process very much.	Individual A
			Setting up trials can bring in new medicines to a country pre-approval.	
			Having more regulatory joint collaborations is a step that can help in the whole complex world of development.	
			If the phase 3 clinical trial included Japan, the drug company can submit to PMDA. If not, they are required to conduct clinical trial and submit new drug approval, creating differences.	Individual C
			Big companies already have a branch in Japan, so they are prepared to conduct clinical trials and drug approval, smaller companies are not.	
			It is always difficult with this data on drug approval differences because a reason might be just that a company chooses not to submit for marketing authorization in other countries.	Individual D
			Look at different approval pathways and international reliance routes to decipher what factors into orphan drug approval.	
	Planning of development processes	Defined timelines	The EMA has strict deadlines but it does not mean you know how long it will take.	Individual B

			You get a fixed amount of time to respond back to the EMA, but it is more connected with how complex the medicine is as for how long it takes.	
			In Saudi Arabia, they tell you directly that if your drug is approved by the FDA or EMA, it is approved straight away.	
			Sometimes organisations have very different sense of time, where other countries have shorter timelines.	Individual A
			PMDA has its targeted duration of a new drug review, which is 12 months for common drugs and 9 months for orphan drugs.	Individual C
			The uniqueness of the UK is that there is no pre-authorization designation, which can be an advantage for companies as they do not have to apply twice.	Individual D
	Financial side of development	Financial incentives	It is very clear that incentives help orphan drugs in the process at EMA, orphan drugs are more likely to get into accelerated programs.	Individual B
			The problem is the money, some orphan drugs are cheap and some are going to be expensive so a country has to decide what to offer incentives.	
			Lower fees for any regulatory intervention in EMA is given, combined with protocol assistance and scientific advice.	
			In a global context, not having financial incentives would stop people from applying at all.	Individual A
			Of course they have a positive influence: small companies have limited budgets and big	Individual C

	companies can reach the market area faster.	
	There is opportunity to get better alignment, an example is that the EMA and the UK offer joint scientific advice.	Individual D
	There is the market exclusivity period of 10 years, which is an important incentive, and there is free scientific advice for UK based companies.	
	Incentives are important vehicles to support companies developing medicines in the rare disease space	

USED QUOTES	INDIVIDUAL A	INDIVIDUAL B	INDIVIDUAL C	INDIVIDUAL D
FIRST QUOTE	"*That's why some of these access or fast track incentives or regulatory convergence, with the FDA and EMA for example, will be really helpful. In terms of policy that can impact drug approval times it is quite specific, it depends on the drug. In a global context I think it would stop people from applying at all, they already don't go to most countries and that is not a friendly environment*."	"*You cannot approve a drug unless the company should meet an application. And the company, sometimes they go to the FDA and it takes them two days to [also] go to Japan. Other times it takes two years, three years or they never even go to Japan.*"	"*Big companies, they already have a branch in Japan, so that they are prepared to conduct clinical trials in Japan and submit to new drug approval in Japan. On the other hand, a small company [located] in the United States, they have no branch in Japan and no crew in Japan, so then it requires a lot of process and resources to prepare the submission in Japan, so that is a big difference. This can cause the approval differences between the*	"*There is opportunity to try to get better alignment around the regulatory and access pathways. So the European Medicines Agency and the UK for example also offer joint scientific advice between medicines, regulators and HTA bodies and that can be a really important tool for helping to develop medicines in a way that the evidence generation fits the*

			United States and Japan."	*requirements of both medicines regulators, but also HTA and payer bodies.*"
SECOND QUOTE	"*Here indeed they look at juggling with cost effectiveness and unmet needs but for rare diseases. When you're talking about a healthcare system, of course there are many, many common conditions, chronic conditions. But with rare diseases you never win with the numbers.* (…) *Sometimes it is economics, but it's also the need of the population that is taken into consideration.*"	"*The fact that it's been approved in another agency helps in some countries. It doesn't help in Europe. But, for example, Saudi Arabia, they tell you directly: "if your drug has been approved by the FDA or by EMA, bring it to us and we approve it straight away." Some countries do that, but they don't say it."*	"*So, I think in such situations it is similar among EU, Japan and United States because if it was a perfect drug, it can fully recover the disease so I understand there [is] no need to make other drugs, but in almost all cases the perfect drug doesn't exist. In many situations one single drug cannot recover the patient, so it is often required to get another drug or additional drugs. So it is not limited to orphan drugs but also for common diseases.*"	"*So from a prevalence perspective, many of the anatomical tumours, so pancreatic, breast or colorectal cancer, many of them are being subsetted into a lot of smaller groups. Which means that actually rare diseases is becoming a difficult term to understand in the era of personalised medicine.*"
THIRD QUOTE	"(…) *the paper is also trying to provide ground for international recognition of the same definition. This [is] so that we can also help drug development, as currently one drug can be orphan*	"*So they can do five things. One of them, they can just be very public: go to the media, say 'this is unfair', another thing that they do is they go and influence the funders. (...) The third one is that they are very*	"*So in the United States, in my understanding, they give orphan designations often in a very early stage of drug development. On the other hand in Japan (...), generally orphan*	"*There are some flexibilities that the UK put in place around using the Reliance Route, which is that straight after Brexit, almost simultaneously UK could copy essentially*

	designated in one country while it isn't in a different country. Of course this is not good if we speak about incentives, as they fit in one country but not the other so that is the discrepancy. We need to have that (same definition) as it is very important and fundamental also for trials of course."	*good at raising money themselves. (...) And the [fourth] thing that they do is they influence the politicians. They go and they talk to their Member of Parliament. (...) The final one is that they try to influence the regulators.*"	*designations are given at a late stage of drug development. So especially the clinical stage of drug development. I think in my understanding EMA is in between with a medium position. (...) The drugs in the clinical stage can relatively easily lead to the final stage of drug development and approval. Many drugs in the earlier stage cannot*."	*what the EU did from CHMP opinion. So in most cases, there wasn't a big gap between those approvals provided that the company applied to the UK. I mean, there's a variety of reasons why companies may not apply to the UK, particularly in rare diseases, and that might be because of reimbursement issues or other kind of issues. So I think the data difference is most likely awaited when the UK left the EU. I assume for the drugs that are before Brexit the timelines would be pretty much the same.*"
FOURTH QUOTE	"(…) *for China, the provinces which are on the East Coast are more wealthy. You know, China is massive and inland the resources are more limited. (...) What*			

happens then is that the coverage is very limited in terms of what is reimbursed and for provinces in the coast, like Shanghai, they actually have their own additional tax. This is to set up like a dedicated rare disease fund to cover some more expensive medicines for patients. What they told us is that actually pharmaceutical companies would then go to these provinces to register and negotiate prices so that they have access to these medicines. That creates some inequity within China, of course it's a massive country, so some would have access, some others don't."

Appendix 7: R Script

1. Load in Data

```
library(readr)
library(dplyr)
library(tidyverse)
library(tibble)
library(rsample)

file.choose()

thesis <- read_delim(file = "C:\\Users\\Gebruiker\\OneDrive\\Bureaublad\\GZW leerjaar 3\\Module 11 - Bachelor opdracht & Data Science\\B
                     delim = ",",
                     col_names = TRUE,
                     col_types = NULL,
                     locale = locale(encoding = "ISO-8859-1"))
```

```
> thesis <- read_delim(file = "C:\\Users\\Gebruiker\\OneDrive\\Bureaublad\\GZW leerjaar 3\\Module 11 - Bachelor opdracht & Data Science\\Bach
elor opdracht\\Approval_data _orphan_drugs_csv.csv",
+                      delim = ",",
+                      col_names = TRUE,
+                      col_types = NULL,
+                      locale = locale(encoding = "ISO-8859-1"))
Rows: 100 Columns: 19
── Column specification ────────────────────────────────────────────────────────────────────────────────────────────────────────────────────
Delimiter: ","
chr (12): Drug name, Type_of_drug, Indication, Type_of_illness, Initial_Approval_Date, FDA_Approval_Date , EMA_Approval_Date, UK_Appr...
dbl  (6): FDA_days_after_initial, EMA_days_after_initial, UK_days_after_initial, AUS_days_after_initial, Japan_days_after_initial, Ca...
lgl  (1): KSA_days_after_initial

i Use `spec()` to retrieve the full column specification for this data.
i Specify the column types or set `show_col_types = FALSE` to quiet this message.
```

2. Acknowledge lack of dates for Saudi Arabia data

```
#Rewrite Saudi Arabia answer of '?'to 'Date unknown'

thesis <- thesis %>%
  mutate(Saudi_Arabia_Approval_Date = recode(Saudi_Arabia_Approval_Date, '?' = 'Date unknown'))
```

3. Count the existing values of variables

```
#count the amount of different answers for Type of drug, Indication and Type of illness

thesis %>% count(Type_of_drug)

thesis %>% count(Indication) %>%
  print(n=83)

thesis %>% count(Type_of_illness)
```

```
> thesis %>% count(Type_of_drug)
# A tibble: 2 × 2
  Type_of_drug       n
  <chr>          <int>
1 Biotech           47
2 Small molecule    53
```

```
> thesis %>% count(Type_of_illness)
# A tibble: 15 × 2
   Type_of_illness                                  n
   <chr>                                        <int>
 1 Inborn errors of metabolism                      7
 2 Rare bone disease                                1
 3 Rare circulatory system disease                  4
 4 Rare developmental defect during embryogenesis   3
 5 Rare endocrine disease                           3
 6 Rare gastroenterologic disease                   3
 7 Rare hematologic disease                        11
 8 Rare hepatic disease                             2
 9 Rare immune disease                              6
10 Rare infectious disease                          3
11 Rare neurologic disease                         10
12 Rare odontologic disease                         2
13 Rare oncologic disease                          38
14 Rare skin disease                                5
15 Rare urogenital disease                          2
```

4. Calculate descriptive statistics of minimum, maximum and mean values

```
#Calculate the min, median, mean & max for days since initial approval per region

summary(thesis$FDA_days_after_initial)
summary(thesis$EMA_days_after_initial)
summary(thesis$UK_days_after_initial)
summary(thesis$AUS_days_after_initial)
summary(thesis$Japan_days_after_initial)
summary(thesis$Canada_days_after_initial)
```

```
> summary(thesis$FDA_days_after_initial)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
      0       0       0     103       0    3662
> summary(thesis$EMA_days_after_initial)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
    0.0    37.0   139.0   220.8   337.0  1217.0      37
> summary(thesis$UK_days_after_initial)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
    0.0   124.5   274.0   396.0   523.5  2936.0      41
> summary(thesis$AUS_days_after_initial)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
   35.0   221.0   306.0   443.0   493.5  2560.0      61
> summary(thesis$Japan_days_after_initial)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
    0.0    91.0   298.0   446.0   769.5  1501.0      77
> summary(thesis$Canada_days_after_initial)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
    0.0   168.0   319.0   389.5   597.5  1414.0      57
```

5. Calculate descriptive statistic standard deviation

```
#Calculate the SD for days since initial approval per region

sd(thesis$FDA_days_after_initial)
sd(thesis$EMA_days_after_initial, na.rm = TRUE)
sd(thesis$UK_days_after_initial, na.rm = TRUE)
sd(thesis$AUS_days_after_initial, na.rm = TRUE)
sd(thesis$Japan_days_after_initial, na.rm = TRUE)
sd(thesis$Canada_days_after_initial, na.rm = TRUE)
```

```
> sd(thesis$FDA_days_after_initial)
[1] 429.7085
> sd(thesis$EMA_days_after_initial, na.rm = TRUE)
[1] 234.6725
> sd(thesis$UK_days_after_initial, na.rm = TRUE)
[1] 471.2647
> sd(thesis$AUS_days_after_initial, na.rm = TRUE)
[1] 453.9106
> sd(thesis$Japan_days_after_initial, na.rm = TRUE)
[1] 426.5602
> sd(thesis$Canada_days_after_initial, na.rm = TRUE)
[1] 297.119
```

6. Calculate mean value when grouping by type of drug variable

```
#Results when grouping by Type of drug

aggregate(FDA_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
aggregate(EMA_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
aggregate(UK_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
aggregate(AUS_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
aggregate(Japan_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
aggregate(Canada_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
```

```
> aggregate(FDA_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
    Type_of_drug FDA_days_after_initial
1        Biotech              187.97872
2 Small molecule               27.56604
> aggregate(EMA_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
    Type_of_drug EMA_days_after_initial
1        Biotech               169.4286
2 Small molecule               285.1071
> aggregate(UK_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
    Type_of_drug UK_days_after_initial
1        Biotech              431.7931
2 Small molecule              361.3333
> aggregate(AUS_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
    Type_of_drug AUS_days_after_initial
1        Biotech               449.5652
2 Small molecule               433.6250
> aggregate(Japan_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
    Type_of_drug Japan_days_after_initial
1        Biotech                492.7143
2 Small molecule                373.2222
> aggregate(Canada_days_after_initial ~ Type_of_drug, data = thesis, FUN = mean)
    Type_of_drug Canada_days_after_initial
1        Biotech                 430.7083
2 Small molecule                 337.4211
```

7. Calculate mean value when grouping by type of illness variable

```
#Results when grouping by Type of illness

aggregate(FDA_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
aggregate(EMA_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
aggregate(UK_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
aggregate(AUS_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
aggregate(Japan_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
aggregate(Canada_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
```

```
> aggregate(FDA_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
                                    Type_of_illness FDA_days_after_initial
1                      Inborn errors of metabolism              293.857143
2                                Rare bone disease              573.000000
3                   Rare circulatory system disease                2.500000
4  Rare developmental defect during embryogenesis                0.000000
5                            Rare endocrine disease              231.333333
6                    Rare gastroenterelogic disease               64.000000
7                          Rare hematologic disease              150.181818
8                              Rare hepatic disease               34.000000
9                               Rare immune disease                0.000000
10                           Rare infectious disease                4.666667
11                           Rare neurologic disease                0.000000
12                          Rare odontologic disease                0.000000
13                            Rare oncologic disease               21.710526
14                                 Rare skin disease              842.200000
15                           Rare urogenital disease                0.000000

> aggregate(EMA_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
                                    Type_of_illness EMA_days_after_initial
1                      Inborn errors of metabolism               188.66667
2                   Rare circulatory system disease               240.75000
3  Rare developmental defect during embryogenesis                 49.00000
4                            Rare endocrine disease                 83.33333
5                    Rare gastroenterelogic disease               149.33333
6                          Rare hematologic disease               172.11111
7                              Rare hepatic disease                 0.00000
8                               Rare immune disease               264.00000
9                            Rare infectious disease               137.50000
10                           Rare neurologic disease               281.25000
11                            Rare oncologic disease               295.45455
12                                 Rare skin disease               107.00000

> aggregate(UK_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
                                    Type_of_illness UK_days_after_initial
1                      Inborn errors of metabolism               782.5000
2                   Rare circulatory system disease               317.6667
3  Rare developmental defect during embryogenesis                175.5000
4                            Rare endocrine disease               284.0000
5                    Rare gastroenterelogic disease               332.3333
6                          Rare hematologic disease               249.7143
7                              Rare hepatic disease                38.0000
8                               Rare immune disease               362.5000
9                            Rare infectious disease               340.0000
10                           Rare neurologic disease               373.1667
11                          Rare odontologic disease               356.0000
12                            Rare oncologic disease               337.6842
13                                 Rare skin disease               887.2000
```

```
> aggregate(AUS_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
                  Type_of_illness AUS_days_after_initial
1      Inborn errors of metabolism              1510.0000
2  Rare circulatory system disease               287.3333
3           Rare endocrine disease               174.5000
4   Rare gastroenterelogic disease               401.5000
5         Rare hematologic disease               196.8000
6             Rare hepatic disease               426.0000
7              Rare immune disease               506.5000
8          Rare infectious disease               332.0000
9          Rare neurologic disease               701.0000
10        Rare odontologic disease               119.0000
11          Rare oncologic disease               340.5714
12               Rare skin disease               899.0000
```

```
> aggregate(Japan_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
                 Type_of_illness Japan_days_after_initial
1 Rare circulatory system disease                68.0000
2          Rare endocrine disease               298.0000
3  Rare gastroenterelogic disease               561.5000
4        Rare hematologic disease               586.8000
5         Rare infectious disease               958.0000
6         Rare neurologic disease               250.3333
7        Rare odontologic disease               984.0000
8          Rare oncologic disease               384.1250
```

```
> aggregate(Canada_days_after_initial ~ Type_of_illness, data = thesis, FUN = mean)
                  Type_of_illness Canada_days_after_initial
1               Rare bone disease                   0.0000
2  Rare circulatory system disease                 182.6667
3           Rare endocrine disease                   0.0000
4   Rare gastroenterelogic disease                 602.3333
5         Rare hematologic disease                 300.4000
6             Rare hepatic disease                 614.0000
7              Rare immune disease                 319.0000
8          Rare infectious disease                 310.0000
9          Rare neurologic disease                 527.7500
10        Rare odontologic disease                 250.0000
11          Rare oncologic disease                 365.2000
12               Rare skin disease                 566.0000
```