MSc (Biopharmaceutical Science) from the Institute of Technology, Sligo

by Denise McDonald, 2018

PROJECT TITLE

A Review of recently Approved Orphan Designation Biological Drugs.

by

Denise McDonald

This project is submitted as part of the requirements for the award of the degree of MSc (Biopharmaceutical Science) from the Institute of Technology, Sligo.

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Course: M.Sc. Biopharmaceutical Science, 2018 **Module:** M.Sc. Thesis

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Abstract

Orphan Drugs are a critical resource for those suffering from rare diseases and there is an urgent need for many new drugs to address the thousands of serious rare conditions which affect millions of people across the world.

The global industry of Orphan Biological Drugs has displayed some growth in recent years, however the number of drugs being approved each year by the FDA and the EMA regulatory authorities remains quite low, with an average of 2 to 3 biologic Orphan Drugs being approved each year.

The regulatory authorities provide incentives to manufacturing companies to research and develop Orphan Drugs, which will often have a small target population. These incentives are crucial to ensure sustained and improved growth in this area.

Many Orphan Biologics are developed and marketed by global multi-national pharmaceutical and biotech companies, after initially being researched by smaller specialist biotechnology companies.

The cost of some Orphan Biologics can be very high, and at times prohibitive for both patients and health providers. This cost can be explained very often by the high cost of drug research and discovery and the higher risk associated with bringing Orphan Drugs to market.

The aim of this thesis is to determine and review the numbers of monoclonal antibodies and other biological products obtaining Orphan Drug approval in both the EU and the US in recent years and the types of companies obtaining approval for these types of drugs. This thesis also looks at costs associated with Biological Orphan Drugs.

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CHAPTER 1 - INTRODUCTION

Biologic drugs are those drugs which are manufactured using biological means (use of living organisms to produce drug product) rather than the traditional chemical manufacture of pharmaceutical compounds. Biological drugs tend to be complex in structure and much more difficult to characterize than traditional chemically manufactured drugs (FDA, What Are "Biologics" Questions and Answers, 2018). Biological drugs can include different types of proteins, monoclonal antibodies, enzymes and hormones, vaccines, blood and blood-derived products and other niche biological products (BLAs, 2015), (FDA, What Are "Biologics" Questions and Answers, 2018) and (Ogbru, n.d.).

Monoclonal antibodies are a particular type of protein drug manufactured in the biotechnology industry.

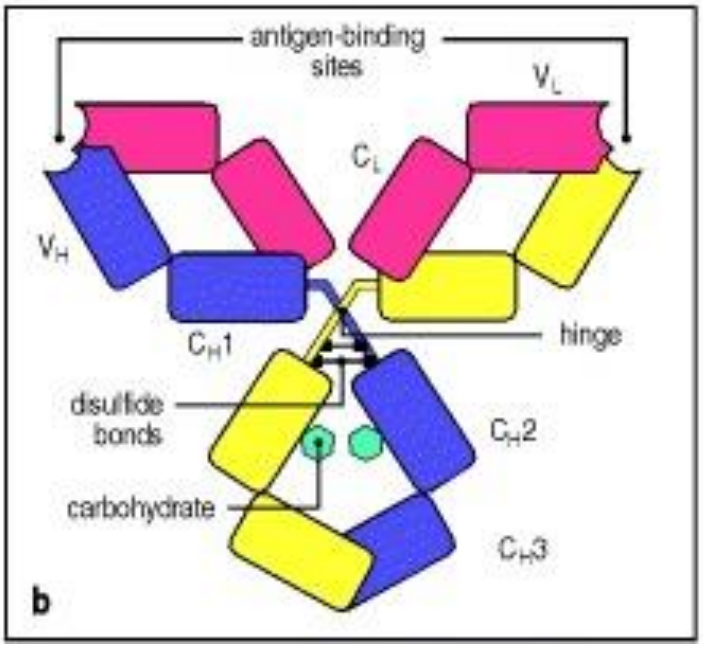

Figure 1.1: Structure of an antibody (Janeway, Travers, Walport, & Shlomchik, 2001)

A monoclonal antibody is an immunoglobulin molecule which is genetically engineered to be produced from an identical group of immune cells, usually by a drug developer (FDA, Guidance

for Industry: Monoclonal Antibodies used as reagents in Drug Manufacturing, 2001). Monoclonal antibodies are designed to act like the body's antibodies in attacking foreign invader cells, primarily cancer cells, in a greatly enhanced capacity (Staff M. C., 2016). Monoclonal antibodies can be designed to work in a variety of ways in the body, including directly destroying cancer cells or targeting cancer cells to facilitate their destruction, preventing growth of cancerous blood vessels and delivering radiation treatment or chemotherapy (Staff M. C., 2016).

Monoclonal antibodies are also important for treating diseases other than cancer, including rheumatoid arthritis (Cohen, Omair, & Keystone, 2013) and multiple sclerosis (Helliwell & Coles, 2009).

Orphan drugs can be defined as drug products which are targeted towards rare diseases and disorders, affecting less than 5 in 10,000 people in the EU (European Medicines Agency Human Regulatory Orphan Designation, 2011) or fewer than 200,000 people in the US (Orphan Drug Regulations, 2013).

Orphan Drugs usually obtain Orphan Designation during the Development Phase of their Drug Lifecycle, through the Drug Approval Process by the Food and Drug Authority (FDA) in the US or the European Medicines Agency (EMA) in the EU. These specially designated drugs retain Orphan Designation for a number of years after approval has been obtained, in addition to other incentives (Act, 2017) (COMP, N/A).

Orphan drugs can be either chemical or biological in nature. Biological Orphan Drugs include both monoclonal antibodies and other biological drugs. Examples of biologic Orphan Drugs which are not monoclonal antibodies are Enzyme Replacement Therapies (Vimizim and Brineura) (both BioMarin products), enzymes and proteins (Alprolix and Strensiq) and Gene Therapy treatments (Strimvelis). Monoclonal antibodies form a large portion of biological Orphan Drugs, which is why they were separated out from other biological Orphan Drugs for this project. Examples of monoclonal antibody Orphan Drugs include Keytruda, Opdivo and Darzalex.

A point of interest for this project is that many Approved Orphan Biological Drugs are produced in Ireland. Production steps may include primary manufacture, secondary manufacture (vial-filling, syringe-filling etc) or packaging. Examples include Vimizim and Brineura (BioMarin Products), Keytruda (an MSD product) and Darzalex (Janssen Biologics), all based in Cork.

Manufacture of Orphan Biologic Drugs in Ireland is a multi-billion dollar industry which is continuing to grow, in areas such as Cork, Dublin and Limerick.

The aim of this project is to research:

- The numbers of mAbs and other biological products with Orphan Drug Designation being approved in both the US and in the EU in recent years (2010 to 2017).
- The reasons for the increase in these numbers in recent years.
- How regulatory approvals of biological Orphan Drugs compare for the same products in the EU and in the US.
- Whether it is mostly Small and Medium Enterprises (SMEs) developing and marketing these Orphan Drug products, due to their projected low volumes or if the majority of recent approved mAb Orphan Drugs are being manufactured by large pharmaceutical companies and the reasons behind this.
- The cost to the patient of biological Orphan Drugs and how this compares to non-Orphan Drugs.

There appears to be a large amount of data available on Orphan Drugs and Orphan Drug approvals, in on-line media articles (some of which will be reviewed briefly in this project). There are also media articles on individual biological Orphan Drugs and their success in terms of patient treatment and in market accessibility.

However, there appears to be no specific information available on trends occurring in the specific sub-section of biological Orphan Drugs and how they contribute to the sector. There appears to be information available on trends of costs of Orphan Drugs in general but not specifically on biological Orphan Drugs.

This project aims to bridge this gap.

Much of the data collated for this project was obtained from on-line research, using either research papers or media and journal articles. All of the regulatory information obtained was from either the FDA or the EMA websites and published articles.

For the purposes of this project, the biological drugs reviewed include different types of proteins, including monoclonal antibodies and enzymes. Other specialist types of biological drugs (such as blood products, stem cells and stem cell therapies and plasma-derived products, tissues etc) will not be looked at as part of this project.

For this project, those biological drugs which are not monoclonal antibodies will be referred to together as '*biologics*' and monoclonal antibody protein drugs will be referred to as '*monoclonal antibodies*' or '*mAbs*'. Together they will constitute the Biological Drugs reviewed in this project.

Pharmaceutical drugs manufactured by chemical means will be referred to as Chemical Drugs, to differentiate them from Biological Drugs.

CHAPTER 2 - LITERATURE REVIEW

2.1 Monoclonal Antibodies

The number of Monoclonal Antibody (mAbs) drugs obtaining Marketing Approval has increased sharply in recent years (Biolabs, 2018) (Biametrics, 2017). The first therapeutic mAb product to be approved was in 1986 and since then over 47 mAb products have received approval worldwide, with this number expected to increase in the coming years (Rodgers & Chou, 2016).

Some of the biggest selling biological Orphan Drugs in the world include the monoclonal antibodies Keytruda (indicated for melanoma cancer treatment and manufactured by Merck, Sharpe and Dohme), Darzalex (indicated for cancer treatment and manufactured by Janssen Biologics) and Yervoy (indicated for treatment for a form of cancer and manufactured by BMS) (Pharma E. , Orphan Drug Report 2017, 2017).

Orphan Drugs are designed to target rare diseases, thus it would be expected that the volume of specific Orphan Drugs being produced would be low and that the cost of research and production of Orphan Drugs may not be recouped by sales for developing companies (FDA, Orphan Drug Act - Relevant Excerpts, 2013). Thus, it may not seem an attractive proposition for many companies to target Orphan Drug production and sales.

Despite this, however, it would appear that the numbers of Orphan Drugs and Biologic Drugs gaining approval in the US and in the EU is increasing in recent years.

In the US alone, more than 400 drugs and biologics have been approved with an Orphan Drug designation since 1983, with numbers increasing in recent years. The FDA approved 49 new drugs with Orphan Designation in 2014 alone (Shelley, 2015), a record number.

Similarly in the EU, almost 400 Orphan Drug designated products were approved by the Committee for Orphan Medicinal Products (COMP) (EMA Orphan Medicines Figures 2000-2015, 2015).

2.2 The Orphan Drug Act

The FDA approved the original Orphan Drug Act (ODA) in 1983 as an incentive to multi-nationals to target drug development and marketing towards serious and rare diseases (Orphan Drug Regulations, 2013). Rare diseases were defined as those diseases which affect less than 200,000 people in the US (Orphan Drug Regulations, 2013) or less than 5 in 10,000 people in the EU (European Medicines Agency Human Regulatory Orphan Designation, 2011).

A drug acquires an Orphan Drug Designation from the approving Regulatory Agency (either the FDA or the EMA for the purposes of this project) during the Development Stage in its Lifecycle, prior to Drug Approval. This means that the drug is being designed with a target rare disease in mind and a with a resulting small target patient population. The timing of the Orphan Drug Designation for new drugs is variable and dependent on the drug, its likely indications and the market conditions (Deneux, Adetona, Pailloux, & Voisin, 2015).

Advantages for companies to obtaining an early Orphan Drug Designation for their product may include:

- early engagement with the Regulatory Authorities,
- securing Orphan Drug Designation incentives or
- as part of a marketing strategy (Deneux, Adetona, Pailloux, & Voisin, 2015).

The authors of this article also outline potential drawbacks to seeking early Orphan Drug Designation for a product, including revelations of a potential product strategy to a public forum and the potential risk of negative regulatory opinions due to insufficient data submitted for a product (Deneux, Adetona, Pailloux, & Voisin, 2015).

The FDA, and indeed the EMA, offer support to companies developing and manufacturing products which have the Orphan Drug Designation (FDA, Developing Orphan Products: FDA and Rare Disease Day, 2011) (EMA, Orphan Incentives, n.d.). These incentives include:

- Scientific Advice and Protocol Assistance,
- Orphan Products Grants,
- Tax Credits,

- Waiver of Prescription Drug User Fees,
- Market Exclusivity etc.

These incentives are offered to encourage research and development in the area of Orphan Drugs, which may potentially have only a small target population once approved (EMA, Orphan Incentives, n.d.) (FDA, Developing Orphan Products: FDA and Rare Disease Day, 2011).

An Orphan Drug Designation for a product at an early stage in its development means that the developing company can benefit from these incentives, which in many cases can amount to a large cost saving or shorter drug approval timelines, in addition to between 7 and 10 years market exclusivity, which can be very beneficial for the developing companies.

Traditionally, pharmaceutical manufacturing companies focused on manufacturing drugs which can target large portions of the population, in order to re-coup the very large costs involved in drug research and development.

The approval of the Orphan Drug Act in 1983 was expected to drive mostly Small and Medium Enterprises (SMEs) towards developing and marketing Orphan Drug products. It was expected that the larger pharmaceutical and biotechnology companies would not have an interest in small volume products with potentially low patient numbers (European Medicines Agency Human Regulatory Orphan Designation, 2011).

There exists up to 7000 rare and serious diseases impacting small populations across the world, with very few treatment options available for some of them (Song, Gao, Inagaki, Kokudo, & Tang, 2012). The Orphan Drug Act was originally set up to incentivize companies to develop and market drugs targeting these rare and serious diseases. In recent years, more and more companies are focusing on discovering and developing drugs for these Orphan Diseases. Regulatory agencies are offering incentives to companies to promote this work (EMA, Orphan Incentives, n.d.) and (FDA, Developing Orphan Products: FDA and Rare Disease Day, 2011).

While many more drugs are getting Orphan Designation and resulting approval, a large number of serious and rare diseases are still without a treatment option for patients (Song, Gao, Inagaki,

Kokudo, & Tang, 2012). In order to address this major issue, more work is required by both the regulators and the developing companies to bring forward new drugs from the research phase through to development and to look at re-purposing old drugs for newer indications.

2.3 Recent Trends in Orphan Drug Approvals

Recent media reports on the pharmaceutical industry have pointed towards the increase in the number of regulatory approvals, and in the commercial success, of Orphan Drugs as a category of the pharmaceutical drugs being approved and produced in the industry in recent years (Ollendorf, Chapman, & Pearson, 2017).

A presentation from the FDA reports on the increased numbers of Orphan Drugs approvals in recent years (Lanthier, Insights into Rare Disease Drug Approval: Trends and Recent Developments, 2017), where 2017 was expected to show a record number of Orphan Drug approvals, as reproduced in Figure 2.1 below (Lanthier, Insights into Rare Disease Drug Approval: Trends and Recent Developments, 2017).

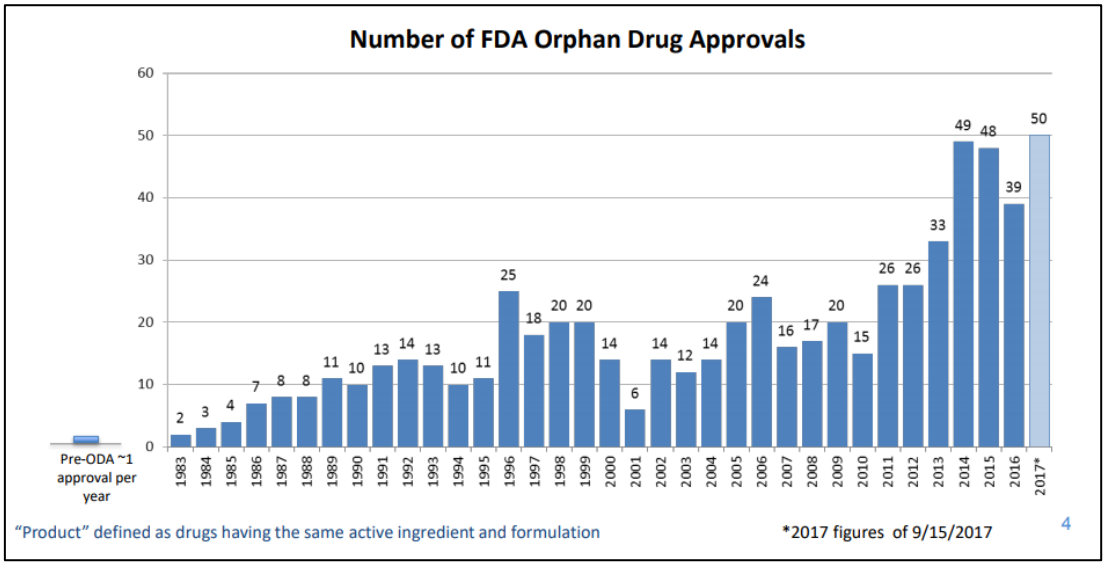

Figure 2.1: Number of FDA Orphan Drug Approvals 1993 - 2017 (Lanthier, Insights into Rare Disease Drug Approval: Trends and Recent Developments, 2017).

The numbers of biologic drugs gaining Orphan Drug approval has increased over the years. The total number of biologic Orphan Drug approvals, as a proportion of overall Orphan Drugs being approved, has increased from 23% in the 1980's to 42% in the 2010's, as reproduced in Figure 2.2 below.

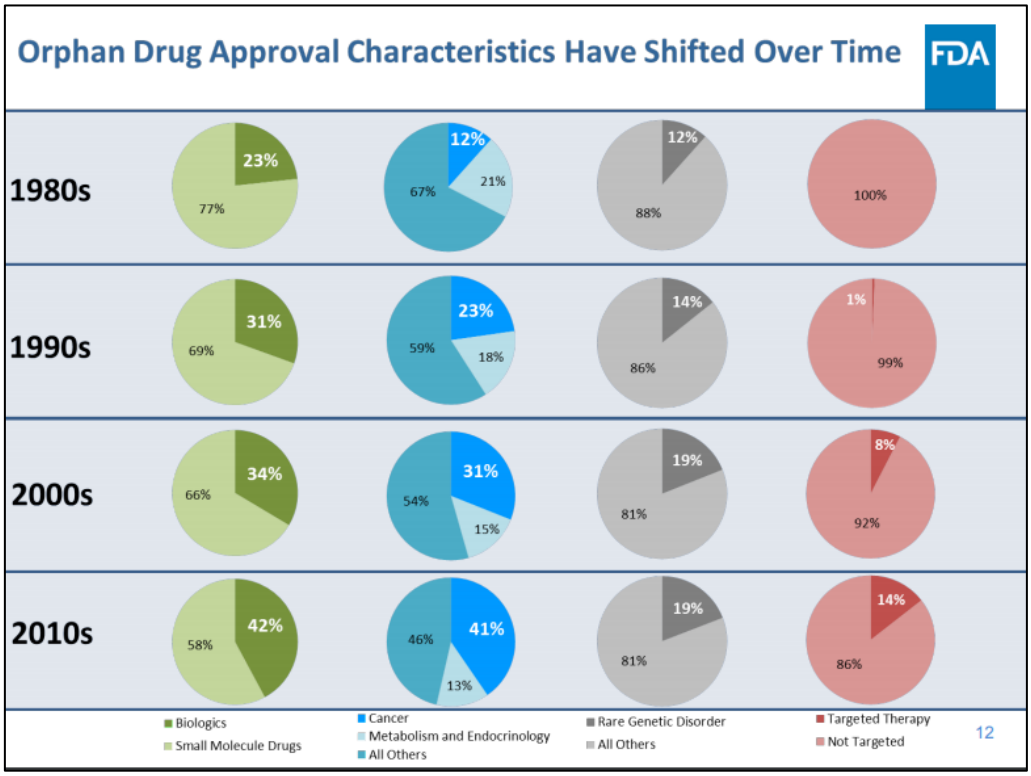

Figure 2.2: Change in Orphan Drug Approval characteristics over time (Lanthier, Insights into Rare Disease Drug Approval: Trends and Recent Developments, 2017).

At the end of his presentation, Lanthier states that the Orphan Drug Act has achieved its goal of incentivizing drug development for rare diseases and increasing the number of Orphan Drug approvals in recent years. He also states that biologics are forming a higher percentage of Orphan Drug approvals over recent years.

The Evaluate Pharma Orphan Drug Report 2017 (Pharma E. , Orphan Drug Report 2017, 2017) looks at recent trends in Orphan Drug Designation and Approval across the US, EU and

Japanese markets and at the companies developing and marketing these specialist drugs. The report highlights the continued growth of the Orphan Drug Market, with sales expected to double in growth in the next five years (to the year 2022) to $209bn and a growth rate of double that of non-orphan drugs. This market growth, along with the very high prices of some Orphan products, will attract further investment in Orphan Drugs by the large pharmaceutical companies.

Figure 2.3 below shows the expected sales increase in Orphan Drugs up to 2022 (Pharma E. , Orphan Drug Report 2017, 2017).

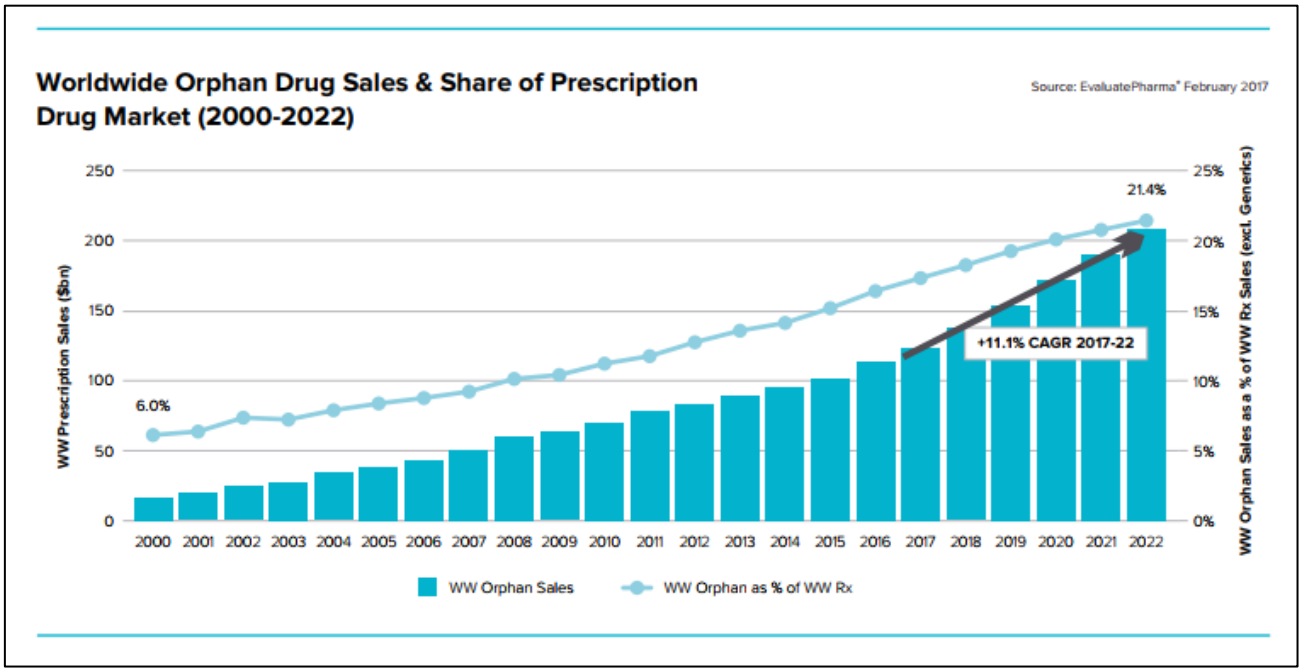

Figure 2.3: Evaluate Pharma 2017 Orphan Drug Report showing predicted increase in OD sales to 2022.

The report states that the average cost of Orphan Drugs per patient per year is over $140,000, while that of a non-Orphan Drug is less than $30,000.

The report highlights that the pharmaceutical company Celgene is expected to top the sales of Orphan Drugs within the next 5 years. Celgene is a global biopharmaceutical company (Celgene,

2017) with headquarters in the US (Celgene Corporation, n.d.) and over 6000 employees worldwide.

The report also states that the monoclonal antibody Opdivo (Nivolumab) will be the biggest selling Orphan Product in Europe within 5 years. The monoclonal antibody Rituxan (rituximab, manufactured by Roche) is currently the second largest selling Orphan Drug in the US.

A table of the top 20 companies in terms of Orphan Drugs Sales from 2016 to 2022 was provided in the report. It is reproduced below:

Evaluate Pharma Report - Worldwide Orphan Drug Sales (2016-2022): Top 20 Companies					
Rank	**Company**	**WW Orphan Sales ($bn) by 2022**	**Rank**	**Company**	**WW Orphan Sales ($bn) by 2022**
1.	Celgene	16.9	**11.**	Sanofi	5.5
2.	BMS	13.5	**12.**	Vertex Pharma	4.8
3.	Novartis	12.0	**13.**	Biogen	4.1
4.	Roche	10.9	**14.**	Actelion	3.8
5.	Johnson & Johnson	10.6	**15.**	AstraZeneca	3.7
6.	Shire	9.8	**16.**	Amgen	3.5
7.	AbbVie	9.6	**17.**	Eli Lilly	3.1
8.	Merck & Co	8.9	**18.**	Bayer Pharma	2.9
9.	Alexion Pharma	6.9	**19.**	BioMarin	2.8
10.	Pfizer	5.6	**20.**	Jazz Pharma	2.7

Table 2.1: Evaluate Pharma Orphan Drug Report 2017 showing predicted Top 20 Pharma Companies by OD sales up to 2022.

The report shows that of the predicted worldwide 20 top-selling Orphan Drugs by 2022, 8 of them will be Monoclonal Antibodies.

The table showing the top selling Orphan Drugs by 2022, along with their Marketing Authorization Holder (MAH), is reproduced from the report below:

Evaluate Pharma Report: Worldwide Top-Selling Orphan Drugs in 2022							
Rank	**Product**	**Name of Active Substance**	**MAH**	**Rank**	**Product**	**Name of Active Substance**	**MAH**
1.	Revlimid	lenalidomide	Celgene	**11.**	Pomalyst	Pomalidomide	Celgene
2.	Opdivo	nivolumab	BMS	**12.**	Gazvya	Obinutuzumab	Roche
3.	Keytruda	pembrolizumab	Merck	**13.**	Opdivo	Nivolumab	Ono Pharma
4.	Darzalex	daratumumab	J&J	**14.**	Jakafi	Ruxolitinib phosphate	Incyte
5.	Soliris	Eculizumab	Alexion Pharma	**15.**	Tasigna	Nilotinib hydrochloride	Novartis
6.	Imbruvica	Ibrutinib	AbbVie	**16.**	Uptravi	Selexipag	Actelion Pharma
7.	Orkambi	Ivacaftor	Vertex Pharma	**17.**	Ocaliva	Obeticholic acid	Intercept Pharma
8.	Imbruvica	Ibrutinib	J&J	**18.**	Ofev	Nintedanib esylate	Boehringer Ingelheim
9.	Yervoy	Ipilimumab	BMS	**19.**	Venclexta	Venetoclax	AbbVie
10.	Rituxan	Rituximab	Roche	**20.**	Niraparib	Niraparib	TESARO

Table 2.2: Evaluate Pharma Orphan Drug Report 2017 showing predicted Top 20 Orphan Drugs by sales up to 2022.

The data in this table shows the increasing trends towards developing Orphan Drugs from monoclonal antibodies and the rise in importance of monoclonal antibodies in treating rare and serious diseases.

The media article '*Five trends shaping rare disease drug development*' (Pagliarulo, 2017) reports on the sudden increase in interest from the industry in developing drugs for rare diseases, with a record 582 requests to the FDA for Orphan Drug designation in 2016, with Orphan Drugs now being regarded as a large part of the business for many large and small drug developers.

The report highlights recent increasing concern over the high cost of some Orphan Drugs, including Spinraza (used to treat the severe and often fatal disease of spinal muscular atrophy) and Exondys 51 (the first drug to treat Duchenne muscular dystrophy), both with costs of over $300,000 a year per patient and queries whether medical insurance companies will continue to pay such high costs in the coming years.

Some reports also highlight the large amount of work done in the industry to discover, develop, obtain approval for and bring to market these specialist drugs which target those rare and sometimes very serious diseases which impact small cohorts of populations globally but can have serious consequences of sufferers. A report from the NORD (National Organization for Rare Diseases) in the US (Diseases, 2017) concludes that the ODA (the US Orphan Drug Act) has been very successful at delivering Orphan Drugs to the market over the past 35 years and that the ODA has been used appropriately by drug companies for the benefit of patients during this time. The report quotes from data just released from QuintilesIMS (a health information technology company) which shows that government spending on orphan drugs forms only a small proportion of overall health spending (Diseases, 2017).

The article '*2016 in review: FDA approvals of new molecular entities'* (Griesenauer & Kinch, 2017) reviews New Molecular Entities (NMEs) approved in 2016 along with their manufacturing companies. The report determined that there was a total of 23 NMEs approved in 2016 by the FDA, a much lower number than expected. The total number of companies currently involved in

pharmaceutical and biopharmaceutical research and development was determined to be 102. This number has fallen from 200 companies in 2004, most likely as a result of Mergers and Acquisitions. The proportion of biologics gaining approval in 2016 was 40%, the highest proportion to date.

The report stated that Orphan Drugs accounted for 40% of all new approvals in 2016 by the FDA, a decrease from 53% in 2015.

From this review, it is clear that there is a greater focus on developing and getting approval for Orphan Drugs from both the manufacturing industry and the regulators. The ratio of Orphan Drug approval to non-Orphan Drug approval has been growing in recent years. There may be several reasons for this increase:

- Improved advertisement and incentives being offered from the Regulatory Authorities to drive Orphan Drug discovery and development (Lantier, 2017).
- Important developments in genetic engineering and technological capabilities in using biologics and monoclonal antibodies as drugs to target and treat a broader range of diseases (Saeed & Awan, 2016).
- Improved focus on treating rare diseases due to the mostly serious impact of these diseases on patients' lives (Staff P. , 2017).
- A realization of the financial benefits to developing and marketing Orphan Drugs on the part of the manufacturing companies (Shelley, 2015).

Whatever the main driver behind this, the continued growth of Orphan Drugs in recent years is broadly welcomed by patient groups and their clinical teams (Diseases, 2017).

This Literature Review highlights the rising cost of some Orphan Drugs [(Capital, n.d.) and (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies, 2017)]. From this initial review, the high cost of some of these Orphan Drugs could be due to a number of reasons:

- The high cost of technology to discover, develop and bring to market some specialist biologic Orphan Drugs.
- The high risk that companies take to invest in developing and marketing Orphan Drugs, many of which may not be successful during the long years of drug discovery and development. The risk of failure at the Proof of Concept stage during drug development can be very high.
- Orphan Drugs are developed for small target populations in mind and thus the recompense for all of the drug discovery and development work for Orphan Drugs must be accounted for in higher prices in comparison to non-Orphan Drugs.

The rising cost of some Orphan Drugs can pose a challenge for Health Insurance companies, Government Health bodies and patients suffering from rare diseases. Various governments and Health bodies are in discussions with marketing companies to bring down the cost of drugs for rare diseases so that more patients can be treated (Tribble & Lupkin, High Prices For Orphan Drugs Strain Families And Insurers, 2017) (Grant, 2017). As Grant notes, some major companies provide one price for a drug to the public and may then negotiate for lower prices with major customers such as private insurance companies and government plans, so it can be difficult to get an exact price for some drugs. She points out that some patients still struggle to access Orphan Drugs due to their high cost**.**

2.4 Types of Companies manufacturing Orphan Drugs

A report which looks at those companies which are involved in the development and marketing of Biological Drugs '*Evaluate Pharma World Preview, 2017'* indicates that mainly large companies manufacture Biotechnology Drugs, as opposed to smaller specialty biopharmaceutical companies, (Pharma E. , Evaluate Pharma World Preview 2017 Outlook to 2022, 2017). It may have been the case that smaller companies specialized to Orphan Drug development and manufacture during the aftermath of the Orphan Drug Act enactment in the US in the 1980's, but it appears that this is no longer the case.

The authors of this report predict that of the top ten companies which manufacture biotechnology drugs by 2022, all of them will be large companies, like Roche, Sanofi, Amgen and Johnson & Johnson (Pharma E. , Evaluate Pharma World Preview 2017 Outlook to 2022, 2017).

The table below shows the list of the top ten companies in terms of sales projected to be manufacturing Biotechnology Drugs in 2022, reproduced from this report (Pharma E. , Evaluate Pharma World Preview 2017 Outlook to 2022, 2017).

Worldwide Prescription Drug Sales from Biotechnology in 2022 – Top 10 companies		
Rank	**Company**	**WW Sales in 2022 ($bn)**
1.	Roche	38.7
2.	Sanofi	24.2
3.	Amgen	21.7
4.	J&J	19.1
5.	AbbVie	19.1
6.	Novo Nordisk	18.4
7.	Merck & Co	17.7
8.	Eli Lilly	14.7
9.	BMS	14.4
10.	Pfizer	14.0

Table 2.3: Evaluate Pharma World Preview Top 10 Biotechnology Companies by 2022 (Pharma E. , Evaluate Pharma World Preview 2017 Outlook to 2022, 2017).

Furthermore, this report showed that of the top selling products in the world by 2022, it is predicted that three Orphan monoclonal antibody drugs will be among the top 11 pharmaceutical

products in terms of sales worldwide (Pharma E. , Evaluate Pharma World Preview 2017 Outlook to 2022, 2017).

As can be seen from the table below (Pharma E. , Orphan Drug Report 2017, 2017), the Approved Orphan monoclonal antibody drugs Keytruda, Opdivo and Darzalex will be among the Top 11 selling drugs in the world by 2022 (Note: These drugs have Orphan Drug status for some rare indications in the US, but do not have this status in the EU).

Top-Selling Products in the World by 2022			
Rank	**Product**	**Active Substance**	**Company**
1.	Humira	Adalimumab	AbbVie + Eisai
2.	Revlimid	Lenalidomide	Celgene
3.	Opdivo	Nivolumab	BMS + Ono Pharma
4.	Keytruda	Pembrolizumab	Merck & Co + Otsuka Holdings
5.	Eliquis	Apixaban	BMS
6.	Xarelto	Rivaroxaban	Bayer + J&J
7.	Imbruvica	Ibrutinib	AbbVie + J&J
8.	Elyea	Aflibercept	Regeneron Pharma, Bayer and Santen Pharma
9.	Ibrance	Palbociclib	Pfizer
10.	Januvia	Sitagliptin phosphate	Merck & Co, Ono Pharma, Almirall and Daewoong Pharma
11.	Darzalex	Daratumumab	Merck & Co, Ono Pharma, Almirall and Daewoong Pharma

Table 2.4: Evaluate Pharma World Preview Top Selling Pharmaceutical Products by 2022

This trend is interesting because historically, the Orphan Drug Act of 1983 was initially designed to target rare disease populations and companies were not expected to profit from these products (Haffner, Orphan Drugs and Drug Pricing in 2017, 2017).

However, a 1984 amendment to this Act allowed manufacturing companies to generate profits on these products. Even so, it was expected that given the anticipated small market share of these drugs, that the profit margins would be low and as a consequence only small enterprises would pursue development and marketing of Orphan Drugs.

The trends in Orphan Drugs has changed in recent years with more and more large companies moving into the sector and they are starting to dominate the market (Pharma E. , Orphan Drug Report 2017, 2017).

The FDA are currently carrying out a review of its Orphan Drug Program '*FDA is advancing the goals of the Orphan Drug Act'*, as part of its Orphan Drug Modernization Plan (Gottlieb, FDA is Advancing the Goals of the Orphan Drug Act, 2017). Part of this review will include the FDA implementing further measures to ensure the incentives offered by the Agency for pursuing Orphan Drug designation are '*consistent with the manner in which Congress intended'*. In addition, the FDA has re-committed itself to supporting research and development of new drugs which target serious and rare diseases.

Nevertheless, there are opportunities for smaller companies to get involved in Orphan Drug development and manufacturing through collaboration with the larger pharmaceutical multi-nationals (Sherry Ku M. , 2015). Examples include Protalix, the small company that discovered the Orphan Biological Drug Elelyso (Protalix, 2018) and is now in collaboration with Pfizer to market the drug, and Imclone Systems Inc, the company behind the development of the monoclonal antibody Orphan Drug Lartruvo. Imclone Systems Inc was acquired by Eli Lilly which now markets the drug which was approved by the EMA and the FDA in 2016 (Bioworld, 2016).

Literature research seems to point towards a shift in the types of companies which are driving the development and marketing of Orphan Drugs, from smaller, niche biotechnology companies to large, multi-national corporations. A number of potential reasons for this change can be deduced from the research carried out in this project:

- Orphan Drugs are specialty drugs that require a large investment to research and develop. Smaller, niche companies may not have the resources to carry out this work, in competition with larger, well-resourced pharmaceutical companies.
- There are so many rare diseases which require medical treatment that it is inevitable that larger companies will be required to participate in the drug discovery and treatment of these illnesses.
- The nature of rare diseases means that cases of them are few and far between across the world. In terms of marketing Orphan Drugs to these diseases, the larger companies have the resources to target drug-delivery on a global scale, compared to smaller, research- or academic-based developers.
- The incentives offered by the regulators to companies developing and marketing Orphan Drugs provide an attractive platform for large companies to get involved in the business.

Whatever the driver towards increased participation of larger companies in the Orphan Drug business, the trend must be welcomed as part of the effort to bring to market much needed treatment for the very many serious and rare diseases affecting populations across the world.

A subsection of the Results Chapter of this project (Section 3.2) investigates if this trend is continued for biologic and monoclonal antibody drugs as a sub-category of Orphan Drugs, for which there doesn't appear to be much specific information available during on-line searches.

While it does appear that most major Orphan Drugs are marketed by large multi-national corporations, there is room for smaller companies to get involved in drug discovery and collaboration with larger companies when it comes to marketing Orphan Drugs on a global scale.

This might particularly be the case with Orphan Drugs in comparison to non-Orphan Drugs as there are so many unmet medical needs in terms of rare diseases that the opportunity to discover and bring to market specialty or niche products can be much greater for smaller companies.

2.5 Regulatory Environment for Approval of Orphan Drugs

The report '*Drug Approvals 2016: Europe vs US'* (Editors, 2017) compares the approvals of New Drugs in the EU and the US for 2016. The report finds that 74 new drug approvals were granted in both the EU and the US, with new drugs being submitted for approval in the US prior to the EU in many cases. The overall number of approvals has decreased in 2016, both by the FDA and the EMA.

The report found that the number of approvals for New Drugs granted to small and medium companies has increased (to 47%) with the larger companies still being granted the greater number of drug approvals (53%).

Another review '*Orphan Drug Designations and Approvals have something to say about Risks'* (Love, 2017) looks at the timeline and the likelihood of the FDA approving Orphan Drugs, once they obtain Orphan Drug Designation during the R&D phase of drug development.

A graph included in this report shows the increase in Orphan Drug Designation in the US from inception of the Orphan Drug Act (1983) to Sept 2017:

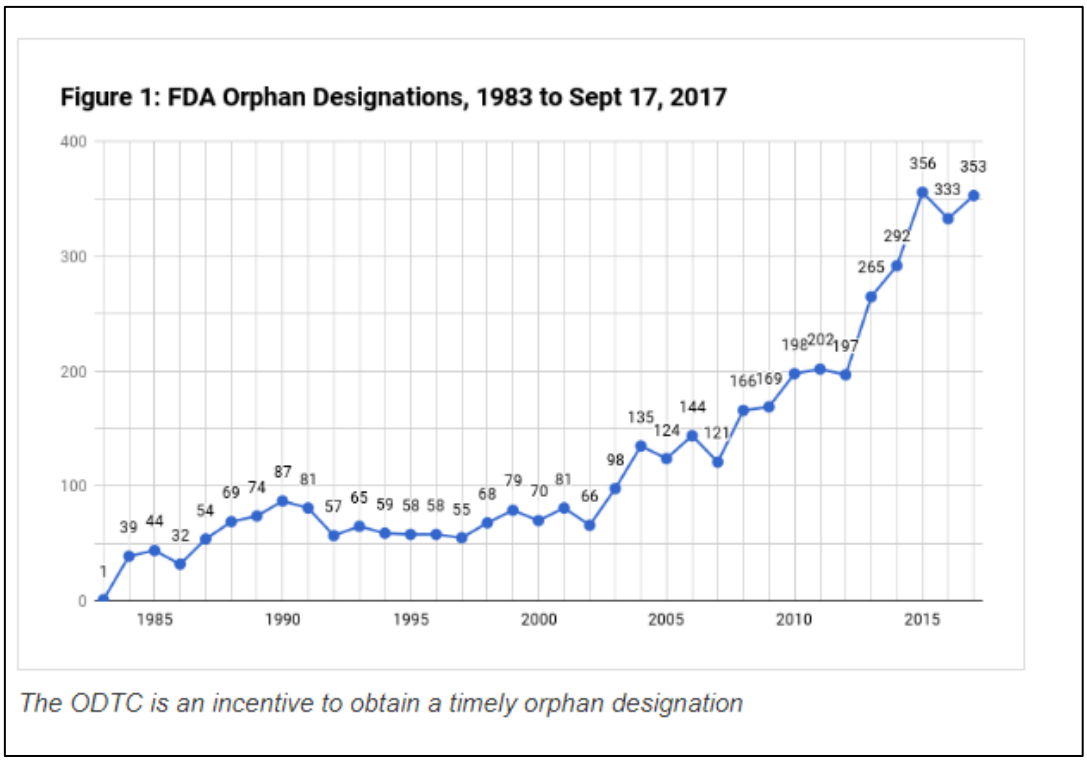

Figure 2.4: FDA Orphan Designations, 1983 to 2017 (Love, 2017).

The average timeline from a drug getting an Orphan Drug Designation to getting FDA Approval was determined to be approx. 5.3 years (Love, 2017). The earlier a drug gets Orphan Drug Designation in its product development lifecycle, the greater the benefit for the drug in terms of financial incentives from the regulatory authorities.

The author of this report calls for more transparency in the initial designation and approval process for Orphan Drugs and the pricing associated with them in each stage as it can be difficult to obtain specific information from on-line sources.

In a report from CDER, the Centre for Drug Evaluation and Research in the FDA and the center responsible for Drug Approvals and applying Orphan Designations to drugs, (Pariser, 2014), the FDA recognize that Orphan Drug Development is the fastest growing area of drug development in recent years. Approx. one third of all New Molecular Entities (NMEs) and Biological License Applications (BLAs) are for Orphan Drug Products.

The key point provided is that while the Orphan Drug Act and the associated approval process does provide incentives for companies to develop and manufacture Orphan Drugs, it does not provide for different or lower standards of quality or results from Clinical Trials. The FDA encourages companies to apply for Orphan Drug Designation early and to keep up good communication between the regulators and the development company.

In the article '*Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen'*, (Giannuzzi, et al., 2017), the authors review the status of Orphan Drugs (both at Designation Stage and Approval Stage) in both the EU and the US.

The review showed that there was a higher level of Designation and Approval of Orphan indications in the US than in the EU. The average yearly values in the US are 93.4 designations and 15.8 approvals for Orphan indications, while the average yearly values in the EU are 79 designations and 8.5 approvals.

The authors point out a number of indications for which there are no Orphan Medications currently available, including renal rare diseases and ophthalmic rare diseases, indicating that there are still growth opportunities that need to be addressed, to ensure as many people suffering from rare diseases have a treatment option.

The report concludes that further cooperation between the regulatory authorities in the US and the EU are required to drive development of Orphan Drugs and to improve treatment options for rare diseases.

The EMA (EMA, Orphan Medicinal Product Designation) defines an Orphan Designation as the following: '*Orphan Medicinal products are for diagnosing, preventing or treating life-threatening or very serious conditions that are rare and affect not more than 5 in 10,000 persons in the EU'*, from Regulation (EC) NO. 141/2000. The EMA provides incentives for R&D of such drugs to developing companies, as the cost of bringing them to market for smaller companies would be prohibitive due to the expected small number of sales of these drugs. Incentives

include Market Exclusivity (10 years exclusivity after approval of MA in the EU, during which time other similar drug products will not be given a Marketing Authorization (MA) for the Orphan Indication), reductions in fees (which can be substantial), assistance with the MA protocol and grants from the EU.

The FDA's Orphan Drug Act of 1983 and its subsequent amendments stipulate that an Orphan Disease is one which '*affects fewer than 200,000 people in the US'*.

In the article '*Orphan Drugs: The Regulatory Environment',* the author (Franco, 2013) reviews the Orphan Drug regulations in different countries, where there is no one agreed definition. Here it is argued that there should be further cooperation between international states on the agreed definition and criteria of Orphan Drugs and on the incentives offered, to entice more companies to start work on R&D of these critical drugs.

From this literature review, it is apparent that there are growing numbers of drugs being designated and approved as Drug over the years and that the Orphan Drug approval rate is becoming a larger portion of Drug Approvals in both the EU and in the US.

It is also clear that further cooperation between the regulatory authorities is required to further drive Orphan Drug development and to ensure the needs of seriously ill people who suffer from rare unmet medical conditions are met in the future.

Orphan Drug regulations, incentives, definitions and pricing strategies need to be agreed and aligned across the regulatory regions, while ensuring that clinical and manufacturing standards for these specialized drugs are maintained at all times.

2.6 Impact of Re-Purposing Drugs as Orphan Drugs

The presentation '*Regulatory Pathway for Repurposed Drugs'* (Karst, 2017) outlines the process of repurposing drugs as follows '*Repurposing generally refers to studying drugs that are already approved to treat one disease or condition to see if they are safe and effective for treating other diseases*', and gives some common examples (Sildenafil and Aspirin). Repurposing drugs is

beneficial for manufacturing companies as it can provide for reduced costs for what is essentially a new drug treatment and can speed up the development and approval process.

The report also details how repurposed drugs can move through the approvals process, types of previously published information which can be used in the approvals process and how changes to the application can be made. These changes can include details of formulation, dosing regimen or use of a combination device. Exclusivity periods may be granted to the applicant for the re-purposed drug, depending on the detail of the application. The exclusivity period for Orphan Drugs is 7 years, the longest of the periods granted.

Extensions to the Food, Drug and Cosmetic (FDC) Act in the US provide incentives to manufacturers to look again at mass market drugs to determine if they could be repurposed for use as Orphan Drugs to treat currently untreated rare diseases.

However, the report highlights that concern has been raised recently in the US Congress surrounding the cost effectiveness of these repurposed Orphan Drugs and questions remain as to whether the Orphan Drug Act will be changed as a result.

The authors of the article '*What price do we pay for re-purposing drugs for rare diseases?'* (Simoens, Picavet, Cassiman, & Dooms, 2012) describe repurposing a drug as where a '*drug for a common disease is later shown to be effective in treating another rare disease*' and in some cases how repurposing drugs can be a desirable option for drug development companies. Obvious benefits include a much reduced cost of R&D and a reduced cost of marketing the drug. However, even with these reduced costs to the company, repurposed drugs for rare disease can be very expensive for the patient.

The report outlines a number of mass market drugs which have been repurposed for Orphan Drugs at a much higher cost than the original drug, including Aztreonam (twice as expensive), Sildenafil (twice as expensive) and histamine (200 times as expensive). In conclusion, the author points to the need for assessing the pricing strategy for re-purposed drugs individually before they become approved for Orphan Designation.

Re-purposing drugs can provide benefits to the patients with rare diseases as much of the drug research and development is already done in terms of safety studies (Simoens, Picavet, Cassiman, & Dooms, 2012). Thus, the lead up to drug approval can be significantly shorter, meaning re-purposed Orphan Drugs can get to market in a much shorter period of time. Clinical Trials for these drugs are still required but make not take at long to complete, due to reduced safety testing requirements. So, it makes sense that effort is put into repurposing more and more commonly used drugs for rare disease applications.

However, strict regulations must be put in place to ensure an increase in pricing for repurposed drugs is kept to a minimum to ensure patient affordability.

2.7 Sales and Cost of Orphan Drugs on the Market

An initial review of literature discussing the pricing of Orphan Drugs showed a level of concern surrounding the high cost of Orphan Drugs to patients. A further in-depth look at these concerns was required for this project, as a result.

A literature review of the pricing structures of Orphan Drugs was carried out. It was difficult to obtain specific and accurate data from scientific papers on the cost of Orphan Drugs as most papers tended to focus on their efficacy and treatment options available for different conditions. In addition, it is difficult to obtain reliable data on the cost of drugs as their cost can vary depending on the country of usage, subsidy by government health departments and dosage and length of treatment of the drug.

Some information was obtained on drug cost and a review is detailed below.

An article by Life Science Capital, an Investor Relations Consultancy based in New York, (Capital, n.d.) entitled '*Analysis of the Orphan Drug Market'* reviewed the market for Orphan Drugs, both chemical and biological. The analysis covered 65 Drugs in the areas of pricing and trends for indications, among other features. The analysis showed that there are strong market sales for Orphan Drugs, in many cases this market is preserved for many years after the drug is approved and even after loss of market exclusivity.

Pricing for Orphan drugs were found to be higher where there were smaller target populations (with drugs prices of approx. $200,000 per patient per year being common for the smaller patient cohort) with lower pricing range for drugs with a higher target population.

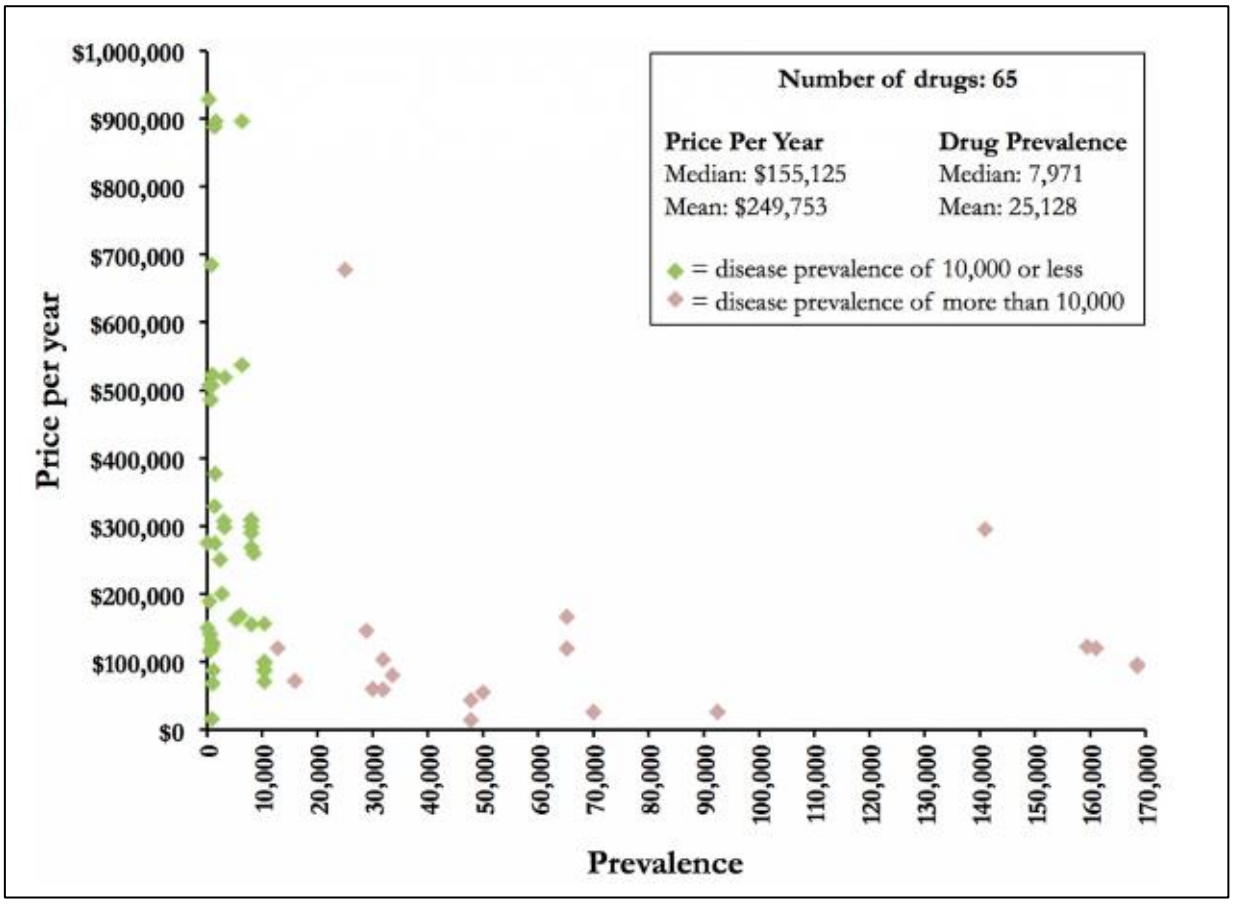

Figure 2.5: Orphan Drug Pricing versus Disease Prevalence (Capital, n.d.).

The report also found that Approved Orphan Biologics were sold at nearly double the price of Approved Orphan small molecule drugs (Small Molecule Drugs are Chemical Drugs). The average price for Approved Orphan Biologics in their review of 65 Orphan Drugs was greater than $320,000 per patient per year, while the average price for Approved Orphan small molecule drugs (chemically manufacturing drugs) was $161,000 per patient per year, half of the price.

The reviewers also found that there is a major advantage in terms of sales to the company who first brings a new Orphan drug to market. Two examples were provided, Sanofi Genzyme's

Cerezyme (first approved in 1994 for treating the rare condition, Gaucher's Disease) and Actelion Pharma's Tracleer (approved in 2001 to treat Pulmonary Arterial Hypertension – PAH).

The report gave further examples of where an Orphan Drug had met or exceeded expectations in terms of patient numbers and speed of uptake of the drug treatment.

Another article published in January 2017, entitled '*Drugmakers Manipulate Orphan Drug Rules to create prized monopolies'* (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules to Create Prized Monopolies, 2017) notes how authorization to market over 400 Orphan Drugs by almost 200 companies has been approved by the FDA in the 30 years since the Orphan Drug Act was enacted. The writers note how the companies' manufacturing these drugs have attached very high prices to them.

Some drugs were approved as Orphan Drugs for a specific rare indication, even though the drug had obtained approval for other general indications initially, such as the bestselling cholesterol drug Crestor, the cancer drug Herceptin and the Rheumatoid Arthritis drug Humira (a monoclonal antibody). This allowed the manufacturing companies to gain the advantages of obtaining the Orphan Drug Designation for their product, such as government grants and market exclusivity for an extended period. According to the authors, there are more than 70 examples of these drugs (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies, 2017).

Other approved Orphan Drugs are allowed to have multiple indications, meaning the number of patients which can be treated with these drugs goes way above the 200,000 patient limit set by the Orphan Drug Act. An example given by the writers was Botox which has millions of patients worldwide but it also has Orphan Drug Designation.

Botox was been given approval by the FDA in 1989 for rare indications such as the treatment of strabismus associated with dystonia in adults and treatment of blepharospasms (ref https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=483 on the FDA website).

The report states that there are many other Orphan drugs approved in this way.

The percentage of Orphan Drugs gaining approval by the FDA has increased from 29% in 2010 to 40% in 2016 (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies, 2017).

Young, Soussi et al analysed the price of Orphan Drugs across Europe in their report '*A Comparative Study of Orphan Drug Prices in Europe*' (Young K. , Soussi, Hemels, & Toumi, 2017). 120 drugs were reviewed across 7 countries. The report outlines how Orphan Drug pricing varies across the EU, as there is currently no agreement among the individual countries on how to price these drugs. This review used the IHS Poli database for pricing the drugs. The IHS PharmaOnLine database is an online pharmaceutical database which facilitates on-line comparison of drug prices across different countries.

The study showed that, in general, the cost of annual treatment with Orphan Drugs in some countries (namely, France, Germany, Italy and Spain) was a little more expensive than in the UK, while the price in other countries (Sweden and Norway), the price was a little less expensive.

The complexity of pricing for Orphan Drugs makes prediction of their price in a particular country more difficult and the authors point out that further study in this area may be required. (Young K. , Soussi, Hemels, & Toumi, 2017).

The article '*Orphan Drugs and Drug Pricing in 2017*' (Haffner, Orphan Drugs and Drug Pricing in 2017, 2017) reviews the history of Orphan Drug pricing in the US and looks at the prices of some of the most expensive Orphan Drugs on the market. The estimated prices of some of the more expensive approved Biological Orphan Drugs are reproduced in the table below:

Orphan Drug Pricing, 2017			
Drug	**MAH**	**Indication**	**Cost**
Eteplirsen	Sarepta	Duchenne Muscular Dystrophy	$300,000
Brineura	BioMarin	Batten's Disease	$375,000-$700,000
Soliris	Alexion	Hemoglobinuria	$420,000
Sprinraza	Biogen	Spinal Muscular Atrophy	$750,000

Table 2.5: Prices reported for some of the highest-price Orphan Drugs (Haffner, Orphan Drugs and Drug Pricing in 2017, 2017).

The author points out the concern that pricing for Orphan Drugs could be getting too high in the US and that price restrictions may end up being put into place by the Regulators. This could have the detrimental effect of reducing manufacturing companies' ability or willingness to pursue further research and development in this area.

The author cautions that balance is required in the area of pricing and price restrictions, so that manufacturing companies can continue to develop new drugs for critically ill patients.

In his article '*Do investors value the FDA Orphan Drug Designation*?' Miller (Miller, 2017) reviews the response of investors to a company which has been granted Orphan Drug Designation (ODA) for a product. Generally, the response of investors has been positive, with an increase in a company's stock price of over 3% once an OD Designation has been granted. This is lower than the price increase observed for drugs being granted Fast Track Designation by the FDA. The author's attribute this to fears by investors that OD Designation is granted at early stages in the drug development process and that a large number of early stage drugs fail in the drug development process. In addition, the market for Orphan Drugs can potentially be very small, leading to concern about their potential marketability.

The study (Picavet, Morel, Cassiman, & Simoens, 2014) '*Shining a light in the black box of orphan drug pricing*' was conducted in 2014 and examined the pricing structures of Orphan Drugs as the pricing mechanisms of these drugs were easily discernible at the time. The study found that lower prices for Orphan Drugs were generally associated with repurposed drugs, drugs which were orally administered and drugs for which other treatment options were available. Orphan Drugs with higher annual costs were associated with drugs for serious illness, those for which no other treatment option is available and drugs which have multiple indications.

Concern has been raised about the ethical aspects of access to Orphan Drugs in the EU and US regions in this article '*Ethical imperatives of timely access to orphan drugs: Is it possible to reconcile economic incentives and patients health needs?*' (Rodriguez-Monguio, Spargo, & Seoane-Vazquez, 2017). The authors point out that increasing numbers of patients with different rare diseases and the high cost of access to many Orphan Drugs are becoming a major issues in terms of access to the necessary healthcare treatments and this is compounded by lack of regulatory alignment between the FDA and the EMA in terms of Orphan Drug incentives, approvals, costs etc. Even with the growing number of Orphan Drugs being approved and the associated economic incentives being offered by the Regulatory Authorities, there are still many rare diseases without treatment options. The authors call for greater cooperation between regulatory agencies and improved focus on patient access to Orphan Drugs and stimulation of the growth of the industry without an increase in the cost of these drugs (Rodriguez-Monguio, Spargo, & Seoane-Vazquez, 2017).

From an initial literature review of the cost of Orphan Drugs to the patient, it would appear that pricing for Orphan Drugs is higher than for non-Orphan designated drugs.

This literature review shows that there are increasing sales for Orphan Drugs over the recent years and that sales of Orphan Drugs can remain high for many years, even after the patent expires. This could be due to the fact that there may not be many other drug options for treating some rare diseases.

The trends which are apparent in this Literature Review appear to show that the pricing of Orphan Drugs is higher when the drug is a specialty drug for smaller patient cohorts. It is difficult to determine a reason for this higher cost but from this Literature Review, it seems as if it could be due to the high costs associated with developing and manufacturing specialty drugs and the high level of expertise and special technological requirements involved.

It would seem that the pricing structure for Orphan Biological Drugs is much higher than that for Orphan Chemical Drugs, sometimes being over twice the cost. This could be due to the higher cost for biological drug development and the higher costs associated with biological drug manufacture. Further research on this area is carried out in this project, in the Results Chapter (Section 3.4 – Review of the Cost of Biologic Orphan Drugs to patients). In addition, research was carried out to determine if there was a difference in pricing between Orphan Biological Drugs and non-Orphan Biological drugs. The outcome is displayed in the Results Chapter of this project (Section 3.4 – Review of the Cost of Biologic Orphan Drugs to patients).

One interesting area of the Literature Review was the way that many common drugs get Orphan Drug approval for some indications and the patient populations for these drugs can number in the millions in some cases. The companies which market these drugs will still get the regulatory incentives and the market exclusivity periods for the rare disease indications. This is an area of the Orphan Drug regulations which needs to be regulated to ensure a fair market and fair accessibility to badly needed drugs for all patient groups. Further research is carried out as part of this project into Orphan Biological Drugs which have extended indications from the original Orphan Indication – the outcome is discussed in the Results Chapter (Section 3.3 – Review of the Extension of Indications for Biologic Orphan Drugs).

The review also seems to show that there is variation in Orphan Drug pricing across countries, another area which should be more tightly regulated.

It does appear that prices for some specialized Orphan Drugs are extremely high, in many cases out of the reach of many patient groups and health departments to pay for them. This in turn can lead to these drugs not being administered to the patients who need them, something which is

detrimental not just to the patients but to the marketing companies of the drugs, as it reduces their marketability across the world. A balance is needed across the regulatory regions around Orphan Drug pricing, to ensure drug availability to all who need them and to ensure continued industry interest and drive towards future drug discovery and development (Picavet, Morel, Cassiman, & Simoens, 2014) and (Rodriguez-Monguio, Spargo, & Seoane-Vazquez, 2017).

It is noted in the EMA Annual Report 2016 (2017, Annual Report 2016, 2017), that drugs are given Orphan Designation because it may not be profitable for companies to market drugs for rare diseases '*under normal market conditions*'. Therefore, a range of incentives is offered to companies to develop drugs for rare diseases, including 10-year market exclusivity, reduction in fees for scientific advice etc. The full range of incentives may not be necessary for larger companies which have resources and scientific capability to develop their own drugs, even for smaller markets.

2.8 CASE STUDY

Glybera (alipogene tiparvovec) was a Gene Therapy treatment for Hyperlipoproteinemia Type I. It was approved as an Orphan Biological Drug in October 2012 by the EMA. It was manufactured by a small biopharmaceutical company, UniQure BioPharma BV, based in Holland. It had an estimated price tag of $1million, per patient (Bioentrepreneur, 2015). Glybera was not submitted to the FDA for approval by the marketing company.

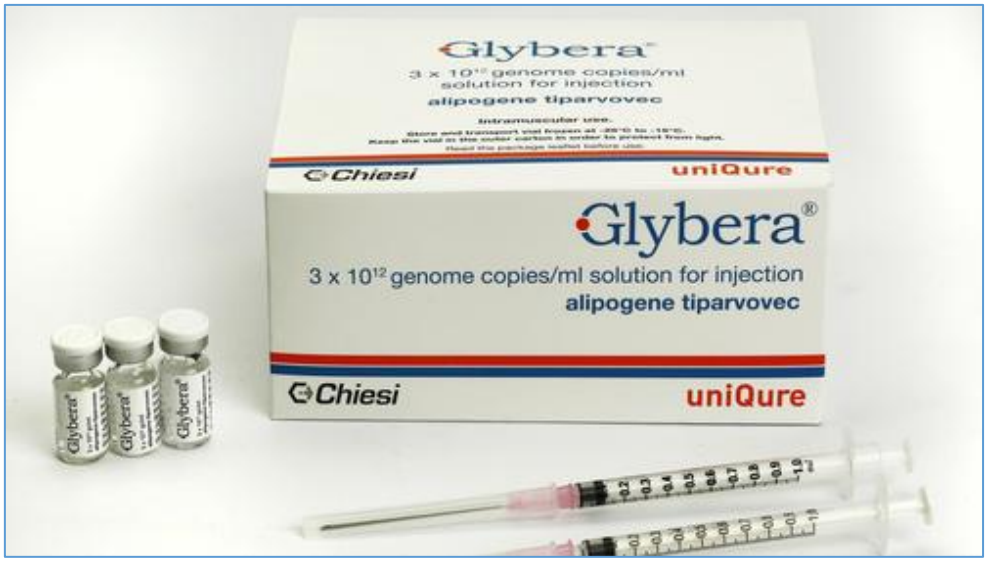

Figure 2.6: Image of Glybera biologic Orphan Drug injections, manufactured by uniQure.

UniQure withdrew the Marketing Application for Glybera from the EMA in October 2017 (uniQure, 2017). The reason given was lack of patient numbers for the treatment. In addition, there would appear to have been regulatory concerns the effectiveness of the drug and the number of patients treated during Clinical Trials (Regalado, 2016). This could have been the reason that the drug was not filed with the FDA for authorization (Regalado, 2016).

This case study shows the risks that companies take in developing and marketing these specialist drugs. Orphan drugs may become approved by the regulatory authorities but may not end up being successful, resulting is high revenue losses to the marketing company.

Clearly, a balance is required between drug cost, target patient numbers, production and R&D costs and company Return on Investment. If drugs are priced too high, they may not have a market and will have to be withdrawn, resulting in high cost to the company. If a drug is priced too low, it may not allow the company to recoup the sometimes very high costs involved in R&D and specialist drug manufacture.

CHAPTER 3 - RESULTS

Section 3.1- Review of Regulatory Approval of Orphan Biological Drugs

This Chapter reviews the Biological Orphan Drugs that have been approved by both the FDA and the EMA from 2010 to the present time, on a year-by-year basis. Both monoclonal antibodies and other biological drugs are included in the review.

The following are excluded from the scope of the project:

- Orphan Biological Drugs approved prior to 2010,
- Orphan Biological Drugs approved in other jurisdictions (other than the US and the EU).

This was done in order to keep the project relevant to the present time and to the EU and US locations.

Details of Data Collection from Regulatory Websites

Data was obtained from each of the regulatory sites on Orphan and non-Orphan Drugs which were approved over the years, as follows:

EMA website

Initial research was conducted utilizing the EMA website *http://www.ema.europa.eu/ema/*. The European Public Assessment Reports (EPARs) for each drug which have been Authorised, Withdrawn, Rejected and Approved by the Agency are detailed on this website.

The EMA publishes a European Public Assessment Report (EPAR) for each centrally approved Marketing Authorization for each product, from which much of the required relevant information was obtained.

EPARs provide a detailed description of each drug and details of the Marketing Authorization Holder (MAH), which is generally the manufacturer for each drug.

The Summary page of all EPARs are displayed alphabetically into 26 sections on the EMA website. These sections can be modified to view the results of the drugs approved under each letter A to Z by Date of Approval or alphabetically. Each drug listing has information on the drug name and Active Substance, Date of Approval, Therapeutic Area, Status and if the drug has a special designation, such as Conditional Approval, Exceptional Circumstances, Biosimilars and Orphan medicines. The EPAR also contains details of Extension of Indications for each drug.

Each of the 26 alphabetical sections was reviewed for Orphan Drugs authorized from 2010 onwards. Blood products and vaccine products were beyond the scope of this thesis and not included.

The resulting biological and monoclonal antibody Orphan Drugs were then catalogued, with information such as Drug Name, Active Substance, Therapeutic Area, Marketing Authorization Holder and Date of Approval.

FDA website

Research into Orphan Drugs approved by the FDA was carried out using the FDA website: *www.fda.gov* and the links '*Drugs*', '*Drug and Biologic Approval and IND Activity Reports*', '*NDA and BLA Approval Reports*' and '*Rare Disease and Orphan Drug Designated Approvals*'. This website provides a listing for all Orphan Drugs approved by the FDA from 2013 to 2016, divided into NDAs (New Drug Applications) for all chemical drugs and BLAs (Biologics License Applications) for all biological and monoclonal antibody drugs.

The Biological Orphan Drugs listed in the BLA Approval Sheet for Orphan Drugs was reviewed and information about each of the approved drugs was collated, with information such as Drug Name, Active Substance, Approved Indication, Approval Date and Sponsor (manufacturer's) Name. Detailed information on each approved drug was also obtained from the FDA website.

Information on approved Chemical Orphan Drugs was collated from the NDA Approval Sheet on the FDA website. For Orphan Drugs approved prior to 2013, the web-link '*New Molecular Entity (NME) Drugs and New Biologic Approvals*' was used.

Under the headings *'Drugs'*, '*Development and Approval Process (Drugs)*' and '*Drug Innovation*', it was possible to review drugs approved in 2017.

Details of the Biological Orphan Drugs approved by the EMA and the FDA in 2017 and 2016 are displayed below.

EMA and FDA Orphan Biologic Drug Approvals 2017

The EMA approved 6 new biological Orphan Drugs in 2017, while the FDA approved 5. The details are shown in **Table 3.1.1** below:

Name of Drug	Active Substance	Indication	Type of drug	MAH	Approval
Besponsa	inotuzumab ozogamicin	Precursor Cell Lymphoblastic Leukemia-Lymphoma	mAb	Pfizer	EMA FDA
Brineura	cerliponase alfa	Neuronal Ceroid-Lipofuscinoses in children	Biologic	BioMarin	EMA FDA
Dinutuximab	dinutuximab beta	Neuroblastoma	mAb	EUSA Pharma UK Ltd	EMA
Natpar	parathyroid hormone	Hypo-parathyroidism	Biologic	Shire Pharma Ireland Ltd	EMA
Oxervate	recombinant human Nerve Growth factor (rhNGF)	Human Nerve Growth factor for Keratitis	Biologic	Dompe Farmaceutici spa	EMA
Bavencio	avelumab	Neuroendocrine Tumors	mAb	Merck Serono Europe Ltd	EMA FDA
Hemlibra	emicizumab	Hemophilia A	mAb	Genentech	FDA
Mepsevii	vestronidase alfa-VJBK	Muco-polysaccharidosis type VII	Biologic	Ultragenyx Pharm Inc	FDA

Table 3.1.1: Details of new Orphan Biologic Drugs authorized by the EMA and the FDA in 2017

Below is a summary of all Orphan Drugs (both Chemical and Biological) authorized by the EMA and the FDA in 2017.

Type of Orphan Drug approved by the EMA and by the FDA in 2017	Number Authorized by the EMA (%)	Number Authorized by the FDA (%)
Chemical	8 (57.1%)	13 (72.2%)
Monoclonal Antibody	3 (21.4%)	3 (16.7%)
Biological, but not mAbs	3 (21.4%)	2 (11.1%)

Table 3.1.2: Summary of all Orphan Drugs authorized by the EMA and the FDA in 2017.

The 8 Chemical Orphan Drugs approved by the EMA in 2017 (EMA, European Public Assessment Reports, 2017) and the 13 Chemical Orphan Drugs approved by the FDA in 2017 (FDA, Novel Drug Approvals for 2017, 2017) are listed in Table 3.1.3 below:

2017 EMA and FDA Approved Chemical Orphan Drugs	EMA or FDA
Lutathera	EMA
Spinraza	EMA
Ledaga	EMA
Cystadrops	EMA
Chenodeoxycholic acid	EMA
Zejula	EMA & FDA
Xermelo	EMA & FDA
Rydapt	EMA & FDA
Macrilen	FDA
Emflaza	FDA
Austedo	FDA
Alunbrig	FDA
Radicava	FDA
Idhifa	FDA
Benznidazole	FDA
Calquence	FDA
Prevymis	FDA
Aliqopa	FDA

Table 3.1.3: List of Chemical Orphan Drugs approved by the FDA and/or the EMA in 2017.

Overall, over 27% (5) of approved Orphan Drugs in the US in 2017 are biological drugs. This compares to over 42% (6) in the EU in 2017.

There is a smaller number of chemical drugs approved as Orphan Drugs (8) in the EU than in the US (13) during 2017.

Table 3.1.4 below is a summary of all drugs authorized by the EMA and the FDA in 2017.

This table shows that only 15.4% of drugs authorized by the EMA in 2017 are Orphan Drugs while a higher proportion (39.1%) of drugs approved by the FDA in 2017 were Orphan Drugs.

Type of Drug authorized by the EMA and by the FDA in 2017	Number Authorized by EMA (%)	Number Authorized by FDA (%)
Orphan	14 (15.4%)	18 (39.1%)
Non-Orphan	77 (84.6%)	28 (60.9%)

Table 3.1.4: Summary of all drugs authorized by the EMA and the FDA in 2017.

The overall ratio of total Orphan Drugs being approved to non-Orphan Drugs is quite low for the EMA in 2017, in comparison to the ratio approved by the FDA in this year.

Overall numbers of Orphan Drugs being approved by the FDA seem to be much higher than those approved by the EMA over the years. This difference is accounted for largely by higher numbers of Chemical Orphan Drugs being approved by the FDA. In addition some biological drugs get standard approval by the EMA while obtaining Orphan Drug status by the FDA. There is more discussion on this trend in later Chapters.

EMA and FDA Biologic Orphan Drug Approvals 2016

Details of all Biological Orphan Drugs authorized by the EMA and by the FDA in 2016 are provided in Table 3.1.5. The EMA approved 3 biological and 2 monoclonal antibody Orphan Drugs in 2016 (a total of 6) while the FDA approved 2 monoclonal antibody Orphan Drugs in 2016 and no biological Orphan Drugs.

Note: Idelvion and Coagadex are not included in the EMA numbers as they are blood products and as such are outside the scope of this project.

Name of Drug	Active Substance	Indication	Type of drug	MAH	Approval
Alprolix	eftrenonacog Alfa	Hemophilia B	Biologic	Swedish Orphan Biovitrum AB	EMA
Darzalex	daratumumab	Cancer Treatment	mAb	Janssen-Cilag International	EMA
Lartruvo	olaratumab	Sarcoma	mAb	Eli Lilly	EMA FDA
Strimvelis	autologous CD34+ enriched cell fraction	Severe Combined Immuno-deficiency	Biologic	GSK	EMA
Zalmoxis	Allogeneic T cells genetically modified	Hematopoietic Stem Cell Transplantation	Biologic	MolMed spa	EMA
Anthim	obiltoxaximab	Anthrax	mAb	Elusys Therapeutics Inc.	FDA

Table 3.1.5: All Biological Orphan Drugs authorized by the EMA and the FDA in 2016.

A summary of all Orphan Drugs authorized by the EMA and by the FDA in 2016 are detailed below in **Table 3.1.6** below:

Type of Orphan Drug authorized by the EMA and by the FDA in 2016	Number Authorized by the EMA (%)	Number Authorized by the FDA (%)
Chemical	7 (58.3%)	7 (77.8%)
Monoclonal Antibody	2 (16.7%)	2 (22.2%)
Biological, but not mAbs	3 (25%)	0

Table 3.1.6: A summary of all Orphan Drugs authorized by the EMA and by the FDA in 2016.

The 7 Chemical Orphan Drugs approved by the EMA in 2016 (EMA, European Public Assessment Reports, 2016) and the 7 Chemical Orphan Drugs approved by the FDA in 2016 listed below in Table 3.1.7.

2016 EMA and FDA Approved Chemical Orphan Drugs	EMA or FDA
Wakix	EMA
Somakit TOC	EMA
Onivyde	EMA
Ninlaro	EMA
Galafold	EMA
Venclyxto (Venclexta)	EMA/FDA
Ocaliva	EMA/FDA
Defitelio	FDA
Spinraza	FDA
Rubraca	FDA
Exondys 51	FDA
Netspot	FDA

Table 3.1.7: Listing of Chemical Orphan Drugs approved by the EMA and/or the FDA in 2016.

In total, 12 Orphan Drugs were approved by the EMA in 2016, compared to 14 2017.

The number of Orphan Drugs approved by the FDA in 2016 was 9. This number increases to 18 Orphan Drugs approved by the FDA in 2017. It is difficult to explain a reason for this discrepancy but the graphs below (**Figures 3.1.1** and **3.1.2**) showing overall numbers of Orphan Drugs being approved by the FDA and the EMA over the years does show variation in trends in the numbers of drugs being approved each year.

Approximately 41% of all Orphan Drugs authorized by the EMA in 2016 were Biological Orphan Drugs. This increased to ~42% in 2017.

Table 3.1.8 below shows a summary of all New Drugs authorized by the EMA and by the FDA in 2016 (EMA, EMA Annual Report 2016, 2017).

Type of New Drug	Number authorized by the EMA in 2016 (%)	Number authorized by the FDA in 2016 (%)
Orphan	12 (48%)	9 (41%)
Non-Orphan New Drug	13 (52%)	13 (59%)

Table 3.1.8: Summary of all New Drugs authorized by the EMA and the FDA in 2016.

This table shows that 48% of New Drugs authorized by the EMA in 2016 were Orphan Drugs, compared to 41% by the FDA in the same year.

The number of Orphan Drugs approved by the FDA in 2016 was 9. This increased to 18 in 2017. This trend is reflected in the graph shown in Figure 3.1.2 below.

On average, the percentage of all Orphan Drugs being approved as a proportion of all Drug Approvals by the EMA is above 30% of all drugs, in recent years while the percentage is nearer to 40% for all Orphan Drugs approved by the FDA in recent years.

Biological drugs and monoclonal antibodies account for at least 40% of all Orphan Drug approvals by the EMA in the last couple of years. That number is closer to 25% for the FDA, due mainly to the larger numbers of Chemical Orphan Drugs being approved by the FDA.

Details for Biological Orphan Drugs approved in the years 2010-2015 are contained in Appendix 1 to this project.

This initial review of data for the years 2016 and 2017 in the EU and US regions shows that there is little variance in the overall numbers of drugs being approved as Orphan Drugs for each year (27 Orphan Drugs approved in 2016 and 2017 in the US, 26 Orphan Drugs approved in 2016 and 2017 in the EU).

There was little difficulty accessing data from either the FDA or the EMA websites. It is clear from the EMA website which drugs are Orphan Drugs and which are not, as each drug has an '*O*' designation beside it. It is necessary to delve into the page of each drug on the FDA website to determine which drugs are Orphan Drugs and which are not.

However, it is easier to determine from the FDA page which drugs are chemical (NDAs) and which are biological (BLAs). There does not seem to be a separate application process on the EMA website for chemical drugs, biological drugs or for Advanced Therapy Medicinal Products (such as Alprolix or Strimvelis). This made the review somewhat more difficult on the EMA website. Advanced biological products (such as vaccines, cell-based products, blood-based products) are approved by CBER (Centre for Biologicals Evaluation and Research) in the FDA, while standard biologics and chemical drugs are all approved through CDER (Centre for Drug Evaluation and Research). There is further discussion of these results at the end of this Section (see Discussion of Results)

Summary of Orphan Drug Approval Numbers, 2010-2017

Data for all Orphan Drugs approved by both the FDA and the EMA was obtained for the years 2010 to 2015. Details results for these years are displayed in Appendix 1. The summary of numbers of Orphan Drugs approved by the FDA and the EMA from the years 2010 to 2017 is shown in **Table 3.1.9** below:

Year	EMA Orphan Drugs			FDA Orphan Drugs		
	Chemical	Biologic	mAb	Chemical	Biologic	mAb
2010	1	1	1	4	4	0
2011	5	0	0	11	2	2
2012	6	1	1	19	2	1
2013	6	0	0	15	0	1
2014	10	1	2	15	2	5
2015	10	3	1	20	3	6
2016	7	3	2	7	0	2
2017	8	3	3	13	2	3
Total	**53**	**12**	**10**	**104**	**15**	**20**

Table 3.1.9: Summary of numbers of Orphan Drugs approved by the FDA and the EMA since 2010.

The EMA has approved 10 monoclonal antibody Orphan Drugs since 2010, along with 12 biologic Orphan Drugs, giving a total of 22 Biologic Orphan Drugs approved by the EMA in this time period. This compares to 20 monoclonal antibody Orphan Drugs and 15 biologic Orphan Drugs approved by the FDA, a total of 35, 13 more than the EMA.

Many of the approved Orphan Drugs are the same for both regulatory authorities but some are different (such as Anthim, Strimvelis and Myalept).

A graphical representation of some of these numbers is given below:

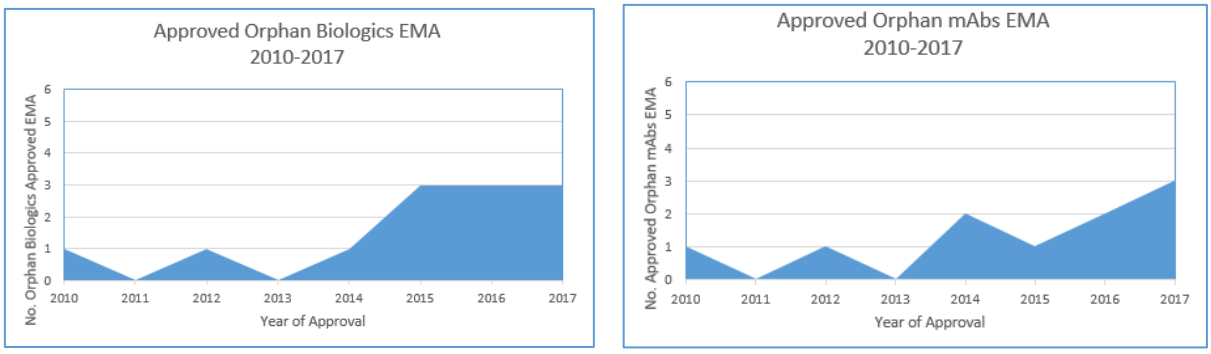

Figure 3.1.1: Graphs showing numbers of biologic and monoclonal antibody Orphan Drugs approved by the EMA since 2010.

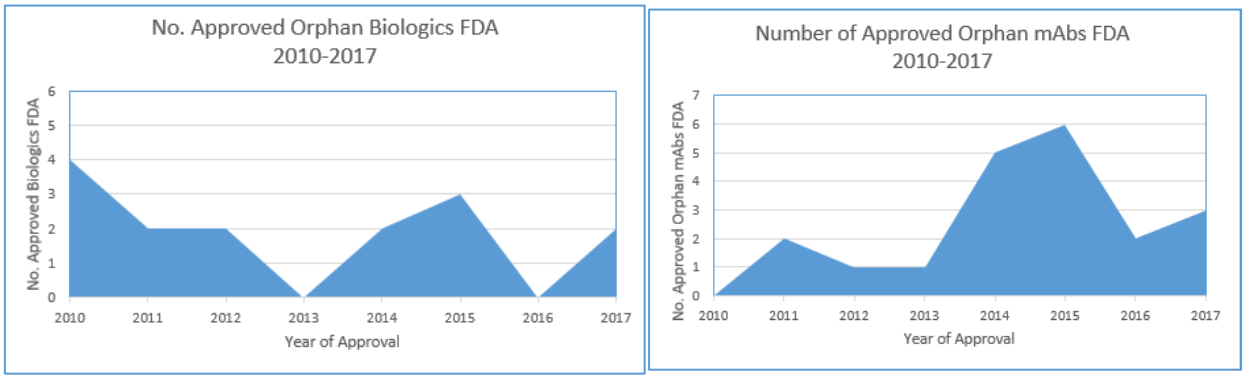

Figure 3.1.2: Graphs showing numbers of biologic and monoclonal antibody Orphan Drugs approved by the FDA since 2010.

As can be seen from these graphs, the number of approvals of biologics and monoclonal drugs as Orphan Drugs has varied over the years but there has been a general but steady rise in approvals by both agencies in the last 5 years. This may be accounted for by the increase in popularity of using biological products for clinical indications, led by the increasing familiarity of both industry researchers and manufacturers in using and developing the technology necessary to make these products from biologic sources.

The FDA has approved 10 more monoclonal antibodies as Orphan Drugs in this time than the EMA and 3 more biologic Orphan Drugs. Upon investigation, it was noted that some of the

monoclonal antibody drugs approved as Orphan Drugs by the FDA during these years were also approved by the EMA, however, they were not given Orphan Drug status in the EMA. Some examples of these drugs include Praxbind, Keytruda, Empliciti, Opdivo, Yervoy and Portrazza. This may explain the discrepancy in numbers of biologic Orphan Drug approval between the FDA and the EMA. There is further discussion on these trends in the Discussion Chapter (Chapter 4, Overall Results and Recommendations) below.

A summary graphic is shown below whereby the total number of Approved Orphan Biologics and monoclonal antibodies by the FDA is compared to those approved by the EMA, between the years 2010-2017.

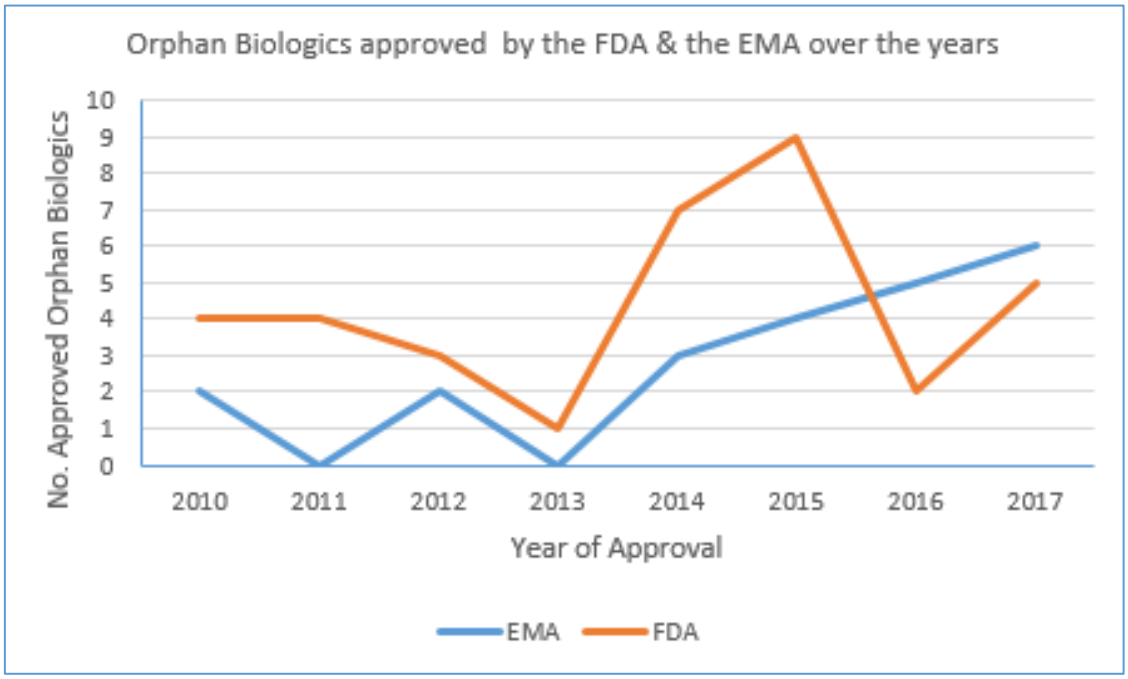

Figure 3.1.3: Numbers of Total Biologic Orphan Drugs approved by the EMA and the FDA since 2010.

This graph shows the dip and then increase in Total Biologic Orphan Drug Approvals over the years with a dip in numbers of Orphan Biologic Drugs being approved by the EMA in 2011 and 2013 and a dip in drugs being approved by the FDA in 2013 and 2016.

The graph also shows the higher numbers of Orphan Biologic Drugs being approved, generally, by the FDA in comparison to the EMA. There is an exception to this trend in 2016 and 2017 when lower numbers of Biologic Orphan Drugs were approved by the FDA in 2016 than in the EMA.

Also, there is an apparent dip in approval numbers in total Biological Orphan Drugs approved in 2013 in both the FDA and the EMA. The reason for this is unclear.

On review of the EMA Annual Report of 2013, there appears to be the usual numbers of drugs obtaining approval from the EMA and no reference to a decrease in Orphan Biologic drug numbers. (Report E. A., 2013)

Comparison to Chemical Orphan Drug Approval

Overall, the number of regulatory approvals for Biologic Orphan Drugs remains relatively low in comparison to approvals for Chemical Orphan Drugs in the past 8 years. This could be due to fact that much of the biotechnology industry for producing clinical medicines is relatively new in comparison to the historical pharmaceutical industry. In addition, the quality requirements and regulations in terms of product characterization, testing and manufacturing are much more stringent for biotechnology products (FDA, What Are "Biologics" Questions and Answers, 2018) and (Bio.org, 2018). This is because the risk of patient infection and the potential for more serious side-effects from intravenously administered drugs is much higher for biological products (FDA, What Are "Biologics" Questions and Answers, 2018). The global biopharmaceutical industry is still growing from a relatively small base 10 years ago and the likelihood is that the percentage of biological drugs being approved will continue to increase in the coming years (Otto, Santagostino, & Schrader, 2014).

The FDA approved 104 Chemical Orphan Drugs in the period 2010-2017.

The EMA approved 53 Chemical Orphan Drugs in the same period.

The FDA approved almost double the number of Chemical Orphan Drugs in the studied time period (2010-2017) in comparison to the EMA.

The graphs shown in Figures 3.1.4 and 3.1.5 below provide a comparison of Chemical and Biological Orphan Drugs approved by both the EMA and the FDA.

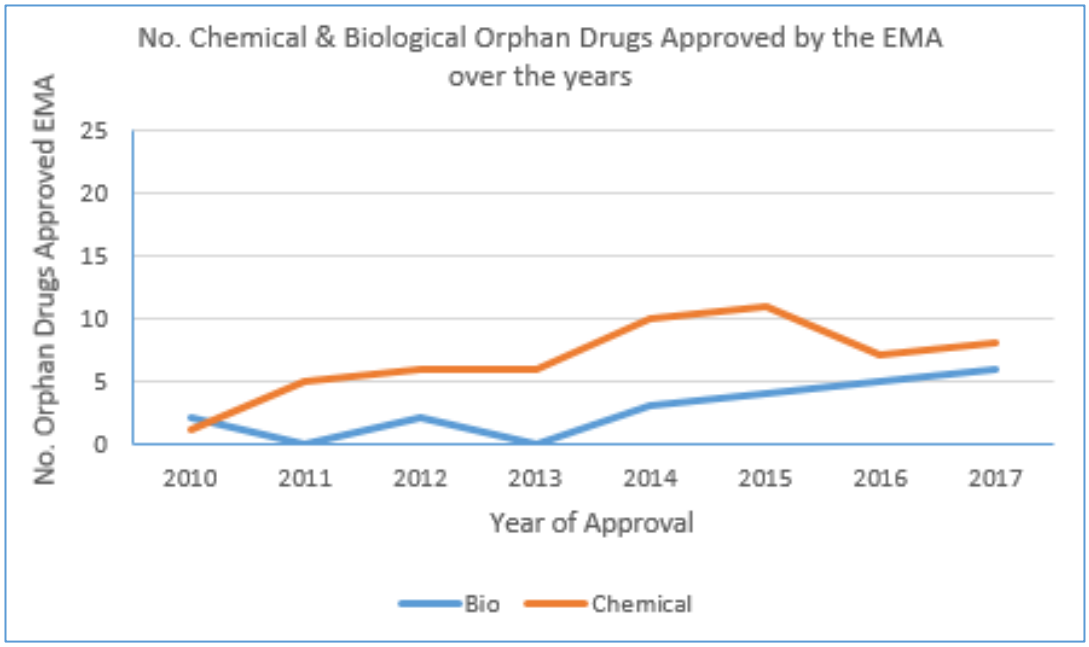

Figure 3.1.4: Numbers of Chemical and Biological Orphan Drugs approved by the EMA for each year since 2010.

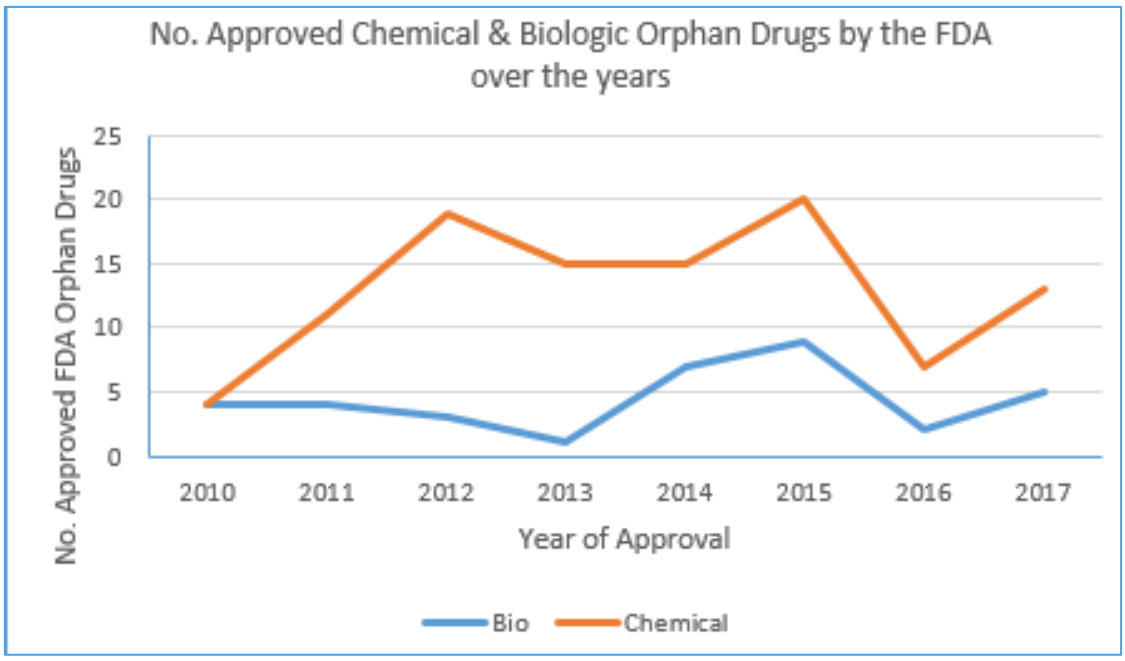

Figure 3.1.5: Numbers of Chemical and Biological Orphan Drugs approved by the FDA for each year since 2010.

The trends reflect the increased numbers of Orphan Drugs obtained approval in the US in comparison to the EU and the higher proportion of Chemical Orphan Drugs being approved over the years in both regions.

There is a discussion on these results below.

Discussion of Results

The year of approval of Orphan Biological drugs was compared for the FDA and the EMA for drugs which were mutually approved. The results are as follows:

- The FDA approved a biologic or monoclonal antibody Orphan Drug *before* the EMA for 16 drugs.

- Some of the drugs were approved by the FDA up to 2 years in advance of the EMA - Natpar was approved by the FDA in 2015 and the EMA in 2017, Unituxin (Dinutuximab) was approved by the FDA in 2015 and the EMA in 2017 and Alprolix was approved by the FDA in 2014 and the EMA in 2016.
- The approval timing were similar for 17 drugs – some of these drugs are Orphan Biologics in the US and standard Biologics in the EU (for example, Kanuma and Strensiq were both approved by the FDA and the EMA in 2015).
- The EMA approved 1 biologic Orphan Drugs in advance of the FDA. This was Besponsa (approved by the EMA in July 2017 and by the FDA in 2016).
- There are similar numbers for approval of Chemical Orphan Biologic drugs, where 25 Orphan Drugs were approved within a year of each other by the two agencies, 15 drugs were approved first by the FDA and 3 first by the EMA.

The EMA have approved some biologic and monoclonal antibody Orphan drugs not approved by the FDA, as follows:

- Nexobrid
- Holoclar
- Strimvelis
- Zalmoxis
- Oxervate

All of these drugs approved in the EU but not in the US are specialist biologic Orphan Drugs, such as cell fractions, growth factors, stem cells or a complex mixture of enzymes in the case of Nexobrid.

These results show that the FDA generally approve biologic and monoclonal antibody Orphan Drugs in advance of the EMA.

This discrepancy was unexpected, given the close working relationship between the FDA and the EMA in reviewing and approving Orphan Drugs. In 2016, the EMA and the FDA announced a new Working Group which would collaborate on drugs for rare diseases, with the aim of promoting development of these drugs (News, 2016). Collaboration would include sharing best practice and regulatory experiences on review and approval of drugs for rare diseases.

In addition, the FDA have approved 69 Chemical Orphan Drugs which do not have approval (either not submitted or not authorized) in the EU, while there are 23 Chemical Orphan Drugs which have approval in the EU but not in the US.

This may be due to the sponsor company policy whereby approval is sought first in the US before the EU for some products. This could be due to the perception that the FDA route is likely to be more successful than the EMA regulatory route or it could be due to other market forces. There does not seem to be clear evidence that the FDA route for drug approval is more successful that starting the process via the EMA (Frost, 2017) although the FDA may approve drugs in general more quickly than the EMA (Kashef, 2017).

It could also be that the Marketing Authorizations are submitted to the FDA and the EMA simultaneously and that there are faster approval times in the US than in the EU rephrase sentence. There is some indication that the review time of New Drug Applications for some products is shorter in the FDA than in the EMA ((Downing, Zhang, & Ross, Regulatory Review of New Therapeutic Agents - FDA versus EMA, 2011-2015, 2017), with the FDA approval of applications taking on average 60 days shorter than the EMA.

This could be due to the fact that the FDA is the sole agency responsible for approving drugs for the US market (a potentially large market) whereas the EMA may have individual countries and regulations to consider before authorizing a drug for central approval.

In addition, the FDA may have set up faster non-standard drug review procedures in comparison to those of the EMA and have better earlier working relationships with drug sponsors throughout the development lifecycle of a drug, allowing for expedited drug development processes (Johansson & Bjurklund, 2017). This is certainly an area that could be reviewed for improvement within the Committee for Orphan Medicinal Products (COMP), the committee

responsible for recommending orphan designation for new drugs in development for rare diseases.

Some approved Orphan Biologic drugs have Orphan Drug Status for some indications in the US but not in the EU. Examples of these cases include Repatha (a monoclonal antibody treatment for Dyslipidemias and Hypercholesterolemia, Repatha has multiple other indications which do not have the Orphan Drug Status), Empliciti (a monoclonal antibody treatment for Multiple Myeloma), Praxbind (a monoclonal antibody treatment for Hemorrhage) and Portrazza (a monoclonal antibody treatment for Carcinoma, Non-Small-Cell Lung Cancer). All of these drugs are approved as standard drugs in the EU for these treatment indications.

In total, the FDA have approved 12 more biologic or monoclonal antibody drugs as Orphan Drugs than the EMA in the timeframe from 2010 (i.e. the EU have approved the drugs but has not given them Orphan Designation) – shown in Table 3.1.10 below.

Drug Name	Indication
Repatha	Heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease
Empliciti	Multiple Myeloma
Praxbind	Uncontrolled bleeding
Portrazza	Metastatic, squamous, non-small cell lung cancer.
Cyramza	Stomach Neoplasms
Myalept	Complications of leptin deficiency
Keytruda	Unresectable or metastatic melanoma
Opdivo	Metastatic squamous non-small cell lung cancer
Raxibacumab	Inhalational Anthrax
Yervoy	Unresectable or metastatic melanoma
Nulojix	Prophylaxis of organ rejection
Xiapex/Xiaflex	Dupuytren's contracture with a palpable cord

Table 3.1.10: FDA approved Orphan Biologic Drugs which are approved but not as Orphan Drugs by the EMA

The reason for this discrepancy across the regulatory regions is unclear.

There is a cross-party working group in the FDA and the EMA which reviews all drugs which have Orphan Drug Designation and which are submitted for approval (FDA E. , 2016). This group is working to develop a common understanding of each other's regulatory approach to reviewing and approving Orphan Drugs and there are monthly meetings between the regulatory

bodies to discuss submissions (Wright, 2016). Thus there would have to be a strong awareness between the regulatory agencies of Orphan Drug regulations and submissions.

It might be expected that there would be strong agreement between both agencies on Drug Approvals and Rejections given the high level of communication and sharing of information, and this may be the case for many high profile drugs. However, according to the terms of reference between the two agencies, there is no obligation that both regulatory agencies both approve or reject the same drugs for approval or for Orphan Drug Designation (EMA T. o., 2016). Similarly, there are differences in approvals and rejections for standard non-Orphan Drugs. Decisions about approvals or not are made by independent assessors in each of the agencies and judgments must comply with the different regulations and legislation across the regions. There could be different interpretations by EU and US regulatory scientists of the same Orphan Drug regulations.

Therefore, it would not be unusual to have some slight differences in scientific judgements and decisions regarding a small number of drugs. This may then result in some of these drugs getting approval or designation in one jurisdiction but not in another.

What is surprising are the number of biological drugs obtaining Orphan Drug Designation by the FDA which have been given only standard drug designation by the EMA. There is a clear trend that more biological drugs get Orphan Drug Designation in the US (reference Table 3.1.9 in this report). Below is a listing of potential reasons for this difference:

- Perhaps the regulations and route to obtaining Orphan Drug Designation for biological drugs are not as stringent in the US as in the EU, even despite the close working relationship between the regulatory agencies.
- Perhaps the incentives to obtain Orphan Drug Designation for sponsor companies are more rewarding in the US than in the EU.
- Perhaps the market for biological Orphan Drugs is larger in the US than in the EU and thus companies are more likely to target the US for Orphan Drug Designation than the EU.

In addition, the FDA have also approved 8 biologic or monoclonal antibody Orphan Drugs which have not been approved by (or not submitted for approval to) the EMA – see table 3.1.11 below.

Drug Name	Indication
Elelyso	Gaucher Disease
Erwinaze	Acute Lymphoblastic Leukemia
Lumizyme	Pompe Disease
Krystexxa	Chronic gout
Hemlibra	Hemophilia A
Mepsevii	Mucopolysaccharidosis type VII
Anthim	Inhalation Anthrax
Voraxaze	Toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function

Table 3.1.11: Biological Orphan Drugs approved in the US but not in the EU.

Thus, 8 drugs were approved as Orphan Drugs in the US in the past 8 years and have not yet been approved in the EU.

This could be due to marketing decisions being made by the Drug Sponsor to target approval in the US first for their Orphan Drug. Sponsor companies may wait to determine trends in the performance of biological Orphan drugs in the US market before submitting it for approval in the EU market. There may be a risk of a rejection for some Orphan Drugs by the EMA if sufficient supporting clinical data is not submitted. Once a drug is rejected by the EMA, it may be much more difficult to obtain a future Authorization of the same drug for marketing.

Since the market for some Orphan Drugs is potentially very small, there may not be sufficient marketing opportunities for some Biological Orphan Drugs in the EU in comparison to the US to justify the investment required to bring an Orphan Drug to market in a second jurisdiction.

This is reflected in the fact that numbers of Biological Orphan Drugs being approved by the EMA and indeed by the FDA continue to be quite low in comparison to Chemical Orphan Drugs.

The number of Chemical Orphan Drugs obtaining approval by both regulatory agencies always exceeds that of the number of biologics Orphan Drugs gaining approval (reference Table 3.1.9 in the report). This is most likely due to the higher numbers of Chemical Orphan Drugs being submitted for approval and the fact that the biologic drugs industry is still in its infancy in comparison to the more traditional chemical pharmaceutical industry.

However, according to the figures in this report (reference Table 3.1.9), the FDA does approve a much higher number of Chemical Orphan Drugs each year than the EMA, as has been observed before (Downing, Zhang, & Ross, Regulatory Review of New Therapeutic Agents — FDA versus EMA, 2011–2015, 2017).

There appears to be broadly similar numbers of biological and monoclonal antibody Orphan Drugs being approved by both agencies:

- 12 biologics and 10 monoclonal antibody Orphan drugs approved by the EMA and
- 15 biologics and 20 monoclonal antibody Orphan drugs approved by the FDA in the time period 2010-2017.

There seems to be equal importance attached to both biologic and monoclonal antibody molecules as options for Orphan Drugs by the manufacturing industry.

This may seem surprising given that monoclonal antibodies, as a class of biological drug, would, perhaps, be better known and more characterized in biopharmaceutical research and manufacturing than the broader class of biological drugs. The science of genetic engineering of

monoclonal antibodies and the manufacturing techniques associated with monoclonal antibodies are well established and have become almost routine at this stage.

The range of other types of biological Orphan Drugs is broad and perhaps, more difficult to characterize and adopt regulations for, so it may be noteworthy that the numbers of these biological Orphan Drugs obtaining approval is similar to the number of monoclonal antibody Orphan Drugs obtaining approval.

However, this does reflect the broad range of rare and serious diseases that require treatment with Orphan Drugs (there are up to 7000 rare diseases estimated in exist in the global population (Song, Gao, Inagaki, Kokudo, & Tang, 2012) and the treatment options may be widely variable for each of them. It is also a reflection of the high level of ongoing research and development in biological drugs occurring in both small academic and research institutions and in large multi-national biopharmaceutical companies.

There is no one size fits all for drug treatment for diseases. Future developments and innovations in the industry and in the associated research and manufacturing technologies will no doubt bring many more new drugs to market in shorter timelines than is occurring currently (Raj, 2014), (Hare, et al., Challenges and strategies in anti-cancer nanomedicine development: An industry perspective, 2017) and (Ozbolat & Hospodiuk, Current advances and future perspectives in extrusion-based bioprinting', 2016).

Section 3.2 – Review of companies manufacturing Orphan Biological Drugs

This Chapter looks at the types of companies discovering, developing and marketing biologic Orphan Drugs and whether the trend observed in the Literature Review Chapter where mostly larger multi-national companies market Orphan Drugs is replicated for the sub-section of biologic Orphan Drugs.

3.2.1 Size of companies manufacturing Biologic Orphan Drugs

For this project, details of biologic and monoclonal antibody Orphan Drugs were collated. It was observed that some of these orphan drugs were manufactured by large multi-national pharmaceutical companies while a smaller number were manufactured by smaller, more specialist biotechnology companies.

As part of this research, an investigation into the types of companies involved in manufacturing Orphan Biologic Drugs was conducted.

In an attempt to categorize the size of companies which manufacture pharmaceutical products, guidelines were drawn up to put a structure around what would constitute a Small, Medium or Large company.

It was decided to select three criteria as descriptors of the companies:

- Number of employees in the company,
- The number of products manufactured by the company and
- The revenue or sales for 2016.

If any of the three criteria for a particular company was not available, two criteria could be used.

The table below was the result.

Company Size	No. Employees	No. Drugs	Revenue	Typical Background of different company size
Small	**Less than 300**	**2 max**	**<$10m**	**Academic/small industry**
Medium	**300-5000**	**3-6**	**$10m-1b**	**Specialist manufacturing**
Large	**>5000**	**>7**	**>1 $Billion**	**Large multi-nationals**

Table 3.2.1: Criteria for determining size of company manufacturing Orphan Drugs

The data in this table was used to determine if the manufacturing company was large, medium or small.

Data on companies was obtained largely from the company's websites or associated websites.

Where a smaller company was a subsidiary of a larger company, details of the larger company only were selected.

Where details of some companies could not be obtained from their websites, alternate websites were used. Sometimes these websites were business/trading websites and sometimes media articles.

Information obtained was as accurate as possible using publicly available information.

Information was also collated on the number of biological Orphan Drugs each company was manufacturing.

Results

The table below shows information collated for a selection of companies. The remainder of the companies are tabulated in Appendix 2.

Company Name	Orphan Biologic Drugs (type)	No. Products by company	No. Employees in company	Revenue/ Sales in Company	Result: Company Size
Novartis	**Arzerra** (mAb)	>50 (Novartis, n.d.)	>24,000 (Novartis, n.d.)	>48bn (USD) (Report N. A., n.d.)	**Large**
Shire Pharma Ireland	**Vpriv** (biologic) **Revestive** (biologic) **Natpar** (biologic)	>20 (Pharma S. , Product List, n.d.)	>23,000 (Pharma S. , Who we are, n.d.)	>11bn (USD) (Pharma S. , Financial Information, n.d.)	**Large**
Dompe Farmaceutici spa	**Oxervate** (biologic)	9 (Farma, RnD Pipeline, n.d.)	600 (Farma, Dompe Discovery Dec 2012, n.d.)	500m (Farma, Dompe Discovery Dec 2012, n.d.)	**Medium**

Table 3.2.2: Details of some companies manufacturing biological Orphan Drugs.

The overall figures for Small, Large and Medium Companies marketing Orphan Biologics and Monoclonal Antibodies for the US and EU markets are outlined in Table 3.2.3 below (with monoclonal antibody and biologics numbers combined).

Company Size	Total Number Orphan Biologic Drugs Approved in 2010-2017 EU and US	Number of Companies
Large	34	21
Medium	6	5
Small	4	4

Table 3.2.3: Summary numbers of different size companies manufacturing biological Orphan Drugs

These numbers are displayed in the bar chart below in Figure 3.2.1.

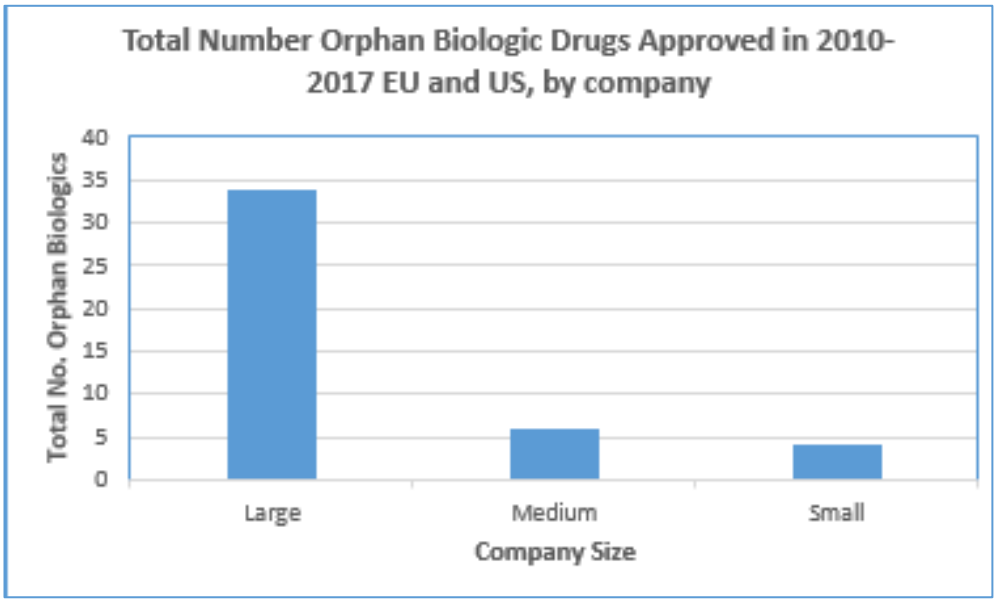

Figure 3.2.1: Numbers of different size companies manufacturing Orphan Biological Drugs for both the EU and US markets.

Figure 3.2.1 indicates that there are mostly large companies authorized to manufacture and market Orphan Biologics and Monoclonal Antibodies in the EU and US Markets (34 companies), with a small number of small and medium enterprises (10 in total) specializing in Biological Orphan Drug manufacture.

In addition, there is some evidence to suggest that smaller companies which originated and developed specialist Orphan Biologic drugs have merged with (or have been acquired by) large multi-national companies or are working with large companies. Examples include the following:

- In 2009, BMS acquired Medarex Inc (BMS, 2009), the company which developed both Ipilimumab (Yervoy) and Nivolumab (Opdivo), both monoclonal antibody Orphan drugs which are used in cancer treatment.
- In 2008, Eli Lilly acquired Imclone Systems, the company which developed the Orphan monoclonal antibody drug ramucirumab (Cyramaza) (Lilly, 2014).

- Pfizer agreed a working arrangement with Protalix, the company which developed the Orphan biologic drug Elelyso used in the treatment of Gaucher's Disease, in 2015 (Garde, 2015).
- In 2012, GSK acquired Human Genome Sciences Inc, the development company of Raxibacumab, a monoclonal antibody Orphan Drug used for the treatment of inhalational anthrax (GSK, 2012).
- The monoclonal antibody Keytruda, approved as an Orphan Drug by the FDA in 2014 for cancer treatment, is marketed by MSD by was originally developed by scientists working for Organon, which was acquired by Schering-Plough in 2007. Schering Plough, in its turn, was acquired by MSD in 2009 (Shaywitz, 2017).
- In 2004, Roche acquired GlycArt, the development company of the Orphan monoclonal antibody Gazyvaro (obinutuzumab) (Roche, 2014) and (Pharma O. , 2005).
- In 2015, Genmab partnered with Novartis and GSK to co-develop ofatumumab (Arzerra) an Orphan monoclonal antibody drug and in 2012, Genmab partnered with Janssen Biotech to develop daratumumab (Darzalex), an Orphan monoclonal antibody drug (Genmab, Genmab Current Partnerships, 2012).
- In 2015, Shire Pharma acquired NPS Pharma, the developing company for the Orphan biologic Revestive (teduglutide) (Shire, 2015).

In all cases cited above, large multi-national companies have taken over the smaller specialist companies and marketed the Orphan Biologic or monoclonal antibody drug(s) originally discovered and developed by the smaller companies.

Discussion of Results

Because of the complexity of biologic drugs in general and specialist biologic Orphan Drugs in particular, it may be mostly small specialist biotechnology institutions and companies which discover and develop the product initially. However, the Orphan Drugs which are more likely to be successful in their development phase are always likely to be viewed as opportunities for investment by larger companies.

The reasons for this are varied.

- Some smaller specialist development companies may have sought collaboration and investment from larger companies to enable them to bring their key product to the marketing stage. Without this investment, it would not be possible for smaller companies to develop drugs for the global market. This is especially the case with Orphan Drugs where the target market may be small and a global patient population is required for Orphan Drugs to be viable.
- In other cases, larger companies may have been seeking opportunities for investment and discovered key drugs being developed by smaller companies and made a business decision to collaborate and work with the smaller company to bring the product from the development stage to the global market.
- It may be viewed by larger multi-national companies that biologic Orphan Drugs are a potential beneficial investment opportunity and they will move to acquire or collaborate with the smaller development companies.
- Larger multi-national companies may have an advantage over smaller specialist biotech companies in that they may have developed better working relationships with the regulatory agencies over the years and have developed extensive knowledge in terms of successfully bringing drugs through the regulatory process.

In any case, without this involvement of the larger companies, these key Orphan Biologic and Monoclonal Antibody Drugs may not have made it to market and many more serious rare diseases would not have available treatment options.

It appears to be the case that the small and medium drug companies which are marketing biologic Orphan Drugs are more likely to be involved in the manufacture of specialist biological drugs aimed at smaller markets, like Anthim which was specially commissioned by the US government for treatment of potential Anthrax infection (Therapeutic, 2017), biological drugs like Nexobrid (treatment for serious burn injuries) and Strimvelis (a stem cell gene therapy, a technology which is still very much in its infancy).

It was the intention of the original Orphan Drug Act in the US and of the Orphan Drug regulations in the EU to incentivize companies to develop and market drugs for rare diseases as '*there is reason to believe that some promising orphan drugs will not be developed unless changes are made…. to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs'*, as described by the FDA Orphan Drug regulations.

According to the 2016 EMA Annual Report, the EMA alone provided €12 million of support for the development of rare diseases (EMA, EMA Annual Report 2016, 2017). This support included assistance with the drug protocols and assessments of applications for Marketing Authorizations.

Since the evidence suggests that large, well-resourced multi-national companies are manufacturing and marketing the majority of biologic Orphan Drugs and that many biologic Orphan Drugs have far exceeded their initial target market in terms of patient numbers (see results from Section 3.2 and results from Section 3.3 below) (FDA, FDA Approved Drug Products for all products, 2017), it would suggest that these companies don't require such incentives or cost reductions to market biologic Orphan Drugs and that the sales alone are sufficient return on the initial high investment costs.

A review is planned for the Orphan Drug regulations in the US later this year, as announced by Scott Gottlieb, Commissioner of the FDA (Gottlieb, FDA is Advancing the Goals of the Orphan Drug Act, 2017). Part of the review will include reviewing the incentives granted by the FDA for drugs designated as Orphan Drug to ensure they are '*consistent with the manner congress intended'* and that the grants are in line with current standards in scientific drug development. This may have the impact of changing the way Orphan Drugs are developed into future but the focus must continue to be on promoting drug discovery in this area to ensure as many rare diseases as possible will have treatment options in the future (Gottlieb, FDA is Advancing the Goals of the Orphan Drug Act, 2017).

The FDA has also refuted the claims that some drug manufacturers are not working towards the public health goals as set out by congress (Lantier, 2017) and have argued that the ODA has been very successful at promoting research and drug approvals for rare diseases.

It would appear from the numbers above that there are a small number of small and medium companies manufacturing Orphan Biologics products. The reason for this could be cost (the high cost associated with developing biologic drugs), complexity (biologic drugs have high levels of complexity which chemical drugs don't have) and a reduction in the number of small companies developing biologic drugs as many of them have been acquired by the larger companies.

The trend appears to be that many small specialist biotechnology companies do discover and start to develop biologic Orphan Drugs. However, larger companies then view these smaller companies as opportunities for merger and acquisition in order to further drive development, manufacturing and marketing of these drugs. Therefore, there is a greater chance that the Orphan Drug will be successfully commercially and will reach more patients with rare diseases, something which is very much in the interest of promoting public health.

Thus, the trend observed in the Literature Review Chapter of this project for Orphan Drugs in general is repeated for biologic Orphan Drugs as a subset of Orphan drugs.

Overall, it is a positive trend for patients with rare diseases as more and more multi-national companies are getting involved in Orphan Drug development and the number of rare diseases with drug treatment is likely to grow in the coming years.

Section 3.3 – Review of the Extension of Indications for Biologic Orphan Drugs

Attention is currently being turned towards Orphan Drugs in general and the trend towards drugs being designated Orphan Drug status, although some Orphan drugs may ultimately be used as a treatment option for a much larger portion of the population than was originally intended by the Orphan Drug Act.

This Chapter aims to determine if this trend is continued for biologic and monoclonal antibody Orphan Drugs.

The FDA enacted the 1983 Orphan Drug Act to address the numerous cases of rare diseases which had unmet medical needs. This act was devised to provide incentives to companies to develop and market drugs for a potentially much smaller market than non-Orphan Drugs. Without incentives, it was believed that there would be little desire to develop and market drugs for rare diseases amongst drug companies (reference the FDA's Orphan Drug Act).

The incentives offered as part of the 1983 ODA include 7-years market exclusivity for that product, tax credits for a large portion of the clinical research costs and waiving of Prescription Drug User Fees (FDA, Orphan Drug Designation Program, 2017).

On review of the approved Orphan Biologic and Monoclonal Antibody Drugs in this report, it was observed that:

- Some Orphan Drugs had extended indications, that is extra indications were sought and approval was given in many cases after the drug had gained initial approval for the Orphan Drug indication.
- Other drugs were in the process of obtaining approval for extra indications from the Regulatory Authorities.
- Some biological drugs had general regulatory approval for some indications and then gained Orphan Drug status for rare disease applications.
- In some cases, Drug Sponsors sought additional indications for their approved Orphan Biologic or Monoclonal Antibody Drugs and were refused authorization.

For this project, data was gathered on extensions to indications for biologic and monoclonal antibody drugs from both the FDA and EMA websites for each drug.

From the EMA website, details of extension of indications for each drug can be found under the tab '*Assessment History*' and the Variations contained in that tab.

In the FDA website, details of extension of indications for each drug can be found (FDA, FDA Approved Drug Products for all products, 2017).

Examples of some extensions are given in Table 3.3.1 below.

Drug	Drug Sponsor	Detail on Extension of Marketing Authorization
Darzalex (daratumumab)	Janssen-Cilag – originally approved in Nov 2015 by the FDA	The FDA extended indications for this product 3 times in 2016 and 2017 (ref here) and the CHMP (Committee for Human Medicinal Products) of the EMA approved an extension of this product in February 2017 (FDA, FDA Approved Drug Products for each product, 2017). The EMA extended the indication for this product in 2017 (refer to Assessment History page for this drug on the EMA website).
Xiaflex	Auxilium Pharms – approved by the FDA in Feb 2010	The FDA granted an extension to the indication for this product in 2013 (FDA, FDA Approved Drug Products for each product, 2017).
Yervoy	BMS – approved by the FDA in March 2011	The FDA granted extensions to the indication for this product in Oct 2015 and in July 2017 (FDA, FDA Approved Drug Products for each product, 2017).
Cyramaza	Eli Lilly – approved by the FDA in April 2014.	The FDA granted an extension to the indication for this product in April 2017 (FDA, FDA Approved Drug Products for each product, 2017).

Table 3.3.1: Details of extensions of indications of some Orphan Biologic Drugs

The details of the remaining biologic and monoclonal antibody Orphan Drugs which have received additional extensions to their indications are listed in Appendix 3.

In total, the FDA have approved 35 biologic and monoclonal antibody Orphan Drugs since 2010. Of these, at least 10 drugs have received extensions of indications, with many more approved Orphan Biologic drugs in Clinical Trials for further indications (reference Appendix 3 for details of those FDA-approved Orphan Biologic drugs with extensions of indications).

This may mean that while many of these Orphan Biologics have Orphan Drug Designation and received the many benefits of that designation, their target population has increased as a result of the additional approved indications, and in some cases number in the many millions of patients.

An example of this latter case include the drug product Repatha (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies, 2017) which has Orphan Drug designation from the FDA but has since broadened its indication base so that the target population is now in the millions.

Repatha (drug substance evolocumab) is a cholesterol lowering drug and was approved by the FDA in 2015 to treat the Orphan Disease homozygous familial hypercholesterolemia (FDA, BLA Approval Repatha, 2015). Repatha is also approved to treat heterozygous familial hypercholesterolemia and can be used to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease. Results from a recent clinical trial which involved over 27,000 patients reports positive benefits from the drug and this could lead to a further growth in patient numbers (Letter, 2017).

Another example is Humira (adalimumab). Humira, manufactured by AbbVie, is one of the largest selling drugs in the world (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies, 2017) and was approved by the FDA in 2002 as a treatment for rheumatoid arthritis (refer to relevant FDA page for details), a condition which affects many

millions of sufferers globally. In 2008 and in later years, the FDA approved Humira for a number of Orphan indications (including juvenile rheumatoid arthritis), meaning that it has Orphan Designation and marketing exclusivity, until 2023.

Thus, it would appear that obtaining an Orphan Designation brings potentially large revenue benefit to the developing/marketing company.

Not all applications for extensions to indications for biologic Orphan Drugs are authorized by the Regulatory Agencies, some are refused. For example Arzerra (ofatumumab, manufactured by Novartis Europharm Ltd) was refused an extension of indication by the EMA in 2016 for extended use as a maintenance treatment for chronic lymphocytic leukemia (EMA, Refusal of a change to the marketing authorisation for, 2016). The EMA's Committee for Medicinal Products for Human Use (CHMP) was concerned that the side-effects of this proposed indication of Arzerra would be more severe than no treatment option with the drug and felt that there was too much uncertainty regarding the benefits of treating patients with Arzerra for this indication. Therefore CHMP refused the extension of indication (refer to EMA website on Arzerra authorisations).

In 2016, the EMA reported that it had adopted extensions of indications for 59 authorised medicines, including those for orphan drugs, such as Adcetris and Gazyvaro (2017, Annual Report 2016, 2017).

Discussion and Results

It does appear that drug companies are moving towards developing and marketing more Orphan Biologics in recent years and attempting to broaden their indication for patients. This can be a positive development for patients as more drugs become available for those suffering from severe and previously un-treatable diseases.

Even if some drugs have standard regulatory approval, there must be an incentive for the company to develop the drug's indication for rare diseases, otherwise there may be no treatment options available.

Drugs companies are not always successful in their R&D activities for extending indications for approved drugs, so there is always a risk involved and there is no guaranteed return on investment for many products or for all the work that is required to bring a drug to a successful New Drug Application stage (EPAR, 2016).

It is clear that incentives are required to encourage research and development into drugs for rare diseases. This is a public service which is carried out by private drug manufacturing companies and one which is very essential to the sufferers of rare diseases. The FDA is currently reviewing the ODA and its goals to enhance the OD approval process and to ensure the ODA grants and incentives to companies to develop and market Orphan Drugs are aligned with the original intent of the Act (Gottlieb, FDA is Advancing the Goals of the Orphan Drug Act, 2017). In addition, the FDA has pointed out that most Orphan Drugs do not acquire extensions of indications to non-orphan conditions, meaning that the cases outlined here are the exception rather than the norm (Lanthier, Insights into Rare Disease Drug Approval: Trends and Recent Developments, 2017)

From the research carried out in other Chapters in this project, it appears that the number of biologic drugs achieving Orphan Drug status in the US is higher than in the EU, where these drugs get approved but don't have the Orphan Drug designation. It is clear that regulations on what should constitute an Orphan Drug are different between the two organizations.

As a compromise towards achieving a balance between incentivizing a company to research and market drugs for rare diseases and the potential large return on investment for a small number of Orphan Biologic Drugs, if the drug is extremely successful for a company for rare disease applications, some reduction in the years of market exclusivity could applied by the regulatory authorities – this is a recommendation from this project. This is just one idea which could satisfy all parties in the Orphan Drug development and approval process.

Section 3.4 – Review of the Cost of Biologic Orphan Drugs to patients

In the Project Literature Review Chapter of this project, the cost of Orphan Drugs was reviewed. There were indications that some Orphan Drugs were very costly and out of the reach for many patients.

The purpose of this next Chapter was to carry out a high level overview of pricing of Biologic and Monoclonal Antibody Orphan Drugs for the patient and to determine if the trend found in the Literature Review is reflected for this subsection of Orphan Drugs.

3.4.1 Cost of Drugs to Patient

It is difficult to obtain public data on the exact cost of drugs to patients (Young K. , Soussi, Hemels, & Toumi, 2017), (Grant, 2017), (Henrard & Arickx, 2016) (Cockerill, Funderburk, & Gaebler, 2017). Pricing differs across countries and may depend on different health insurance plans and plans put in place by Health Authorities. In addition, some drugs are only needed for a short duration (less than 5 doses over a period of about 2-3 weeks) while others need to be administered for much longer periods (some drugs must be administered for life). Also, some drugs are administered to patients based on patient weight and therefore dosage differs for each patient. It was therefore difficult to get an exact comparison on cost across various drugs.

However, an attempt was made to obtain approximate pricing to the patient for Orphan Biologic Drugs, based on publicly-available data, such as that from reputable online journals or, failing that, from medical or industrial on-line media reports. Most cost data was obtained for up to 1 year supply of the drug (annual cost) but where that information was not available, cost was taken for shorter duration of supply of a drug. This part of the project does lack strict scientific rigor as there is a reliance on online media articles for much of the information. However, the aim of this Chapter is to obtain a general overview of Orphan Biologic Drug pricing at the current time, rather than obtaining exact cost information on each drug in each country, for a specific treatment period, which would be outside the scope of this project.

Attempts were made to contact Irish Health Insurance companies for drug pricing information but this level of detail was considered commercially sensitive and was not shared.

All of the cost data available was for minimum pricing of drugs. Most of the drugs would cost more to administer over long-term or for multiple doses.

Results of Cost Ranges of Biologic Orphan Drugs

Below is a sample of data collected for the biologic and monoclonal Orphan Drugs approved by the FDA or the EMA in the period 2010-2017. Data for the remaining drugs is outlined in Appendix 4.

Drug (Type)	Approximate Cost per year	Reference	Cost Range
Arzerra (mAb)	$50-120,000	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227992/	$50-100,000
Vpriv (biologic)	~$170,000pa	https://secure.medicalletter.org/w1337d	$150-200,000
Strensiq (biologic)	>$360,000	http://www.pharmatimes.com/news/nice_restricts_nhs_access_to_alexions_366k-a-year_bone_drug_1185995	$200-400,000
Bavencio (mAb)	~$150,000pa	https://www.bloomberg.com/news/articles/2017-03-23/pfizer-and-merck-kgaa-s-new-cancer-drug-to-cost-13-000-a-month	$100-150,000

Table 3.4.1: Approximate cost of some biologic Orphan Drugs to the patient

The summary cost range data of most of the biologic and monoclonal antibody Orphan Drugs approved by the FDA and/or the EMA in the time period 2010-2017 (with the exception of the

drugs named above) is displayed in **Table 3.4.2** below. The total number of drugs analysed was 40. Details of some drugs were not included due to difficulties in obtaining references to drug pricing.

Approximate Cost Range per year	No. Approved Orphan Biologic Drugs	% of Total
<$50K	7	17.5
$50-100K	8	20.0
$100-150K	9	22.5
$150-200K	5	12.5
$200-400K	6	15.0
$>400K	5	12.5
Total	**40**	

Table 3.4.2: Summary of approximate costs of approved Orphan Biologic Drugs to the patient

A bar chart of this data is shown in **Figure 3.4.1** below, with cost ranges divided into <$50,000, $50-100,000, $100-150,000, $150-200,000, $200-400,000 and over $400,000.

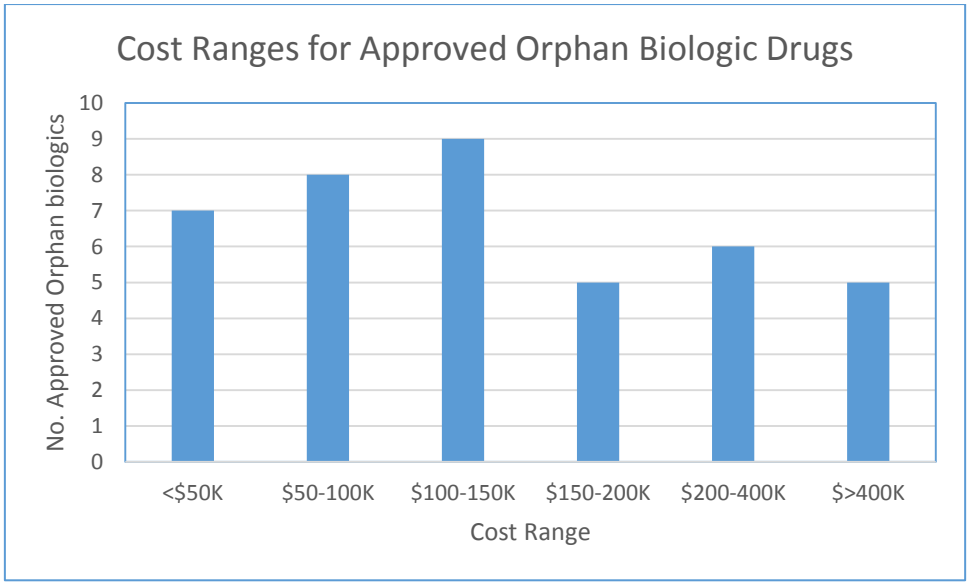

Figure 3.4.1: Bar Chart representing cost ranges of approved Orphan Biologic Drugs

The data shows that over 17% of these drugs have a cost range of less than $50,000 per year. Over 60% of these drugs have a cost range of over $100,000 per year, with over 27% having a cost range of over $200,000 per year (with a proviso that these are the minimum prices shown for most of these drugs).

Results of Cost Ranges of Chemical Orphan Drugs

For comparison purposes a number of Chemical Orphan Drugs were analysed on a similar cost basis. There are larger numbers of Chemical Orphan Drugs so only a sub-section was chosen, as follows - the drugs selected were drugs approved from recent years (2014 - 2017).

Again, it was difficult to obtain information on the cost of many Chemical Orphan Drugs, so only those with freely available cost information were used.

The results of some of the cost ranges for 34 Chemical Orphan Drugs approved by the FDA or the EMA in the years 2014-2017 are displayed in **Table 3.4.3** below. The same cost ranges as above were chosen for comparison purposes.

Further results for Chemical Orphan Drugs approved by either the FDA or the EMA in the years 2014-2017 are displayed in Appendix 4:

Chemical Drug	Approval Date	Cost of Drug	Cost Range	Reference
Ledaga	Mar 17	>$3000	<$50,000	file:///C:/Users/Denise/Downloads/T7S0706_E_PICAVET.pdf
Spinraza	May 17	>$100,000	$100-150,000	https://www.nytimes.com/2016/12/30/business/spinraza-price.html
Ninlaro	Dec 2016	>$9000	<$50,000	https://www.drugs.com/price-guide/ninlaro https://www.drugs.com/monograph/ninlaro.html
Zejula	Mar 17	>$15,000	<$50,000	https://www.drugs.com/price-guide/zejula https://www.drugs.com/dosage/zejula.html
Radicava	May 17	>$140,000	$100-150,000	https://alsnewstoday.com/2017/05/18/things-to-know-about-the-new-als-drug-radicava/

Table 3.4.3: cost ranges of some approved Chemical Orphan Drugs

The summary of results of the 34 of the Approved Chemical Orphan Drugs (approved in the FDA and/or the EMA) are shown in **Table 3.4.4** below. Other Chemical Orphan Drugs approved in this timeframe are not shown as no cost was available.

Cost Range	No. Approved Orphan Chemical Drugs 2014-2017	% of Total
<$50K	16	47.1
$50-100K	6	17.6
$100-150K	7	20.6
$150-200K	2	5.9
$200-400K	3	8.8
$>400K	0	0.0
Total	**34**	

Table 3.4.4: Summary of cost ranges of approved Chemical Orphan Drugs

A bar chart of this data is shown below:

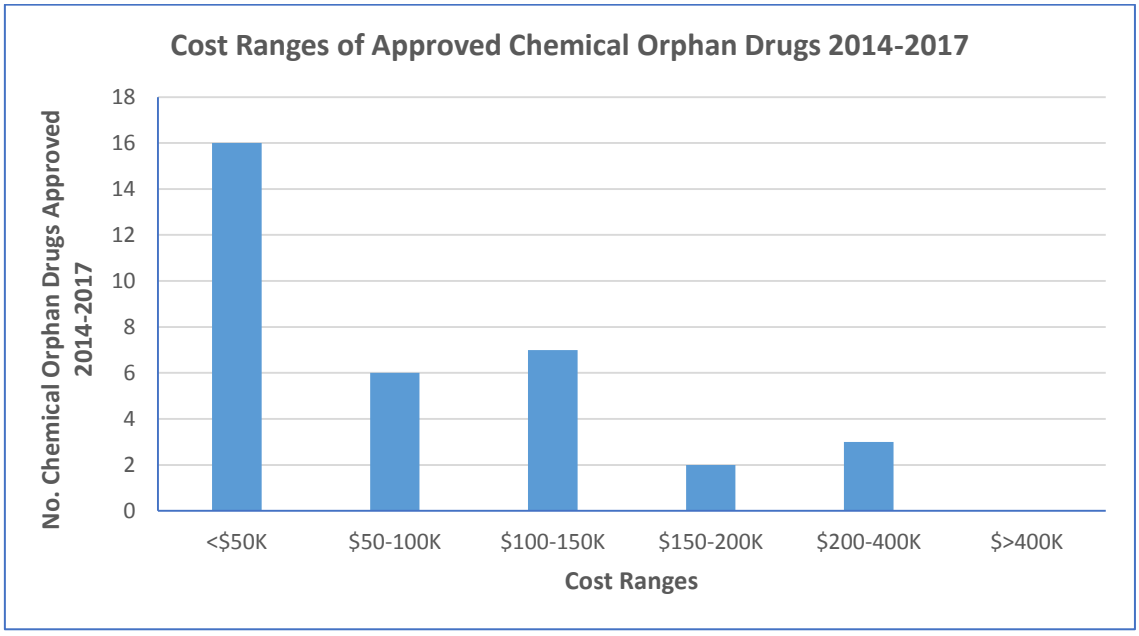

Figure 3.4.2: Bar Chart representing of cost ranges of approved Chemical Orphan Drugs

As can be observed from this bar chart, 47% of the approved Chemical Orphan Drugs have an annual cost price range of less than $50,000, compared to just 17.5% of Biologic Approved Orphan Drugs. Just over 35% of Approved Chemical Orphan Drugs have a cost range of above $100,000, compared to over 60% of Approved Biologic Orphan Drugs.

Both cost ranges are displayed for comparison in a single bar chart below:

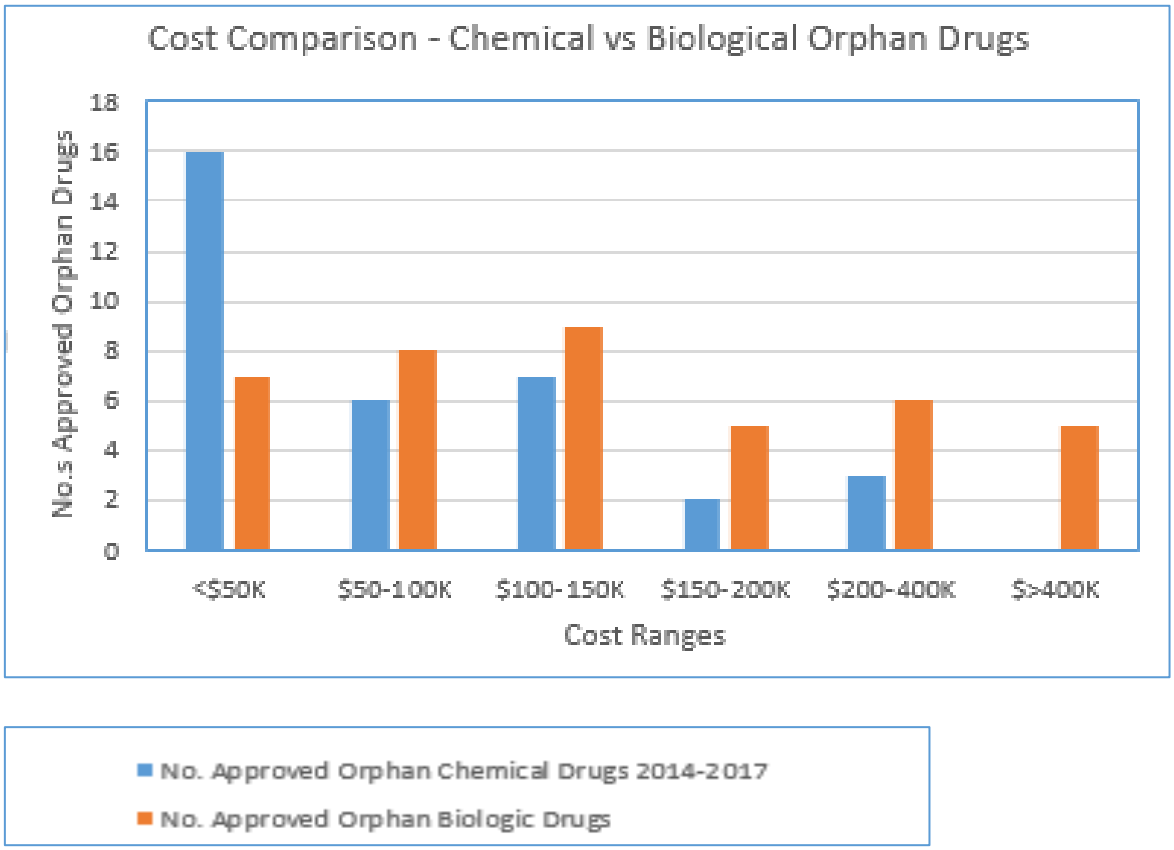

Figure 3.4.3: comparison of cost ranges of approved Chemical and Biological Orphan Drugs

This shows that a larger proportion of Chemical Orphan Drugs have cost ranges in the lower brackets (below $50,000 per patient per year) while the Biological Orphan Drugs seem to have the higher cost ranges.

Results of Cost Ranges of biologic non-Orphan Drugs

Finally, a review of the cost of 21 Non-Orphan Biological Drugs approved by EMA and/or the FDA in the time period 2013-2017 was carried out for comparison purposes.

The results of some of these cost ranges are shown in the table below.

Further results are displayed in Appendix 4.

Drug	Year Approved	Approx Cost per year	Cost Range	Reference
Gardasil 9	2015	$540 per injection	<$50,000	www.getgarded.ca/faqs
Tecentriq (atezolizumab)	2016	Up to $12,500 per month, >$150,000 pa	$100-150,000	www.bioworld.com/fda-approves-genentechs-duo-tecentriq+diagnostic-for-bladder-cancer
Truxima (rituximab)	2017	Over $900 pm, >$10,000 pa	<$50,000	www.drugs.com/priceguide-rituxan
Tremfya (guselkumab)	2017	$58,000	$50-100,000	www.seekingalpha.com/johnson&johnsons-tremfya-a-potential-blockbuster-drug
Trumenba (Meningococcal Group B Vaccine)	2017	~$100	<$50,000	www.cdc.gov/vfc/awardees/vacccine-price-list
Zinplava (bezlotoxumab)	2016	£2470 per dose, ~$3350	<$50,000	www.nice.org.uk/advice/chapter/preventing-recurrence-of-clostridium-difficile-infection-bezlotoxumab

Table 3.4.5: Cost ranges of some approved biologic non-orphan drugs

The results of the review of these 21 drugs is shown in the table below:

Cost Range	No. Approved Non-Orphan Biologic Drugs (2014-2017)	% of Total
<$50K	13	61.9
$50-100K	5	23.8
$100-150K	1	4.8
$150-200K	1	4.8
$200-400K	0	0.0
$>400K	1	4.8
Total	**21**	

Table 3.4.6: Cost ranges for 21 approved biologic non-orphan drugs

A bar chart of this data is shown below:

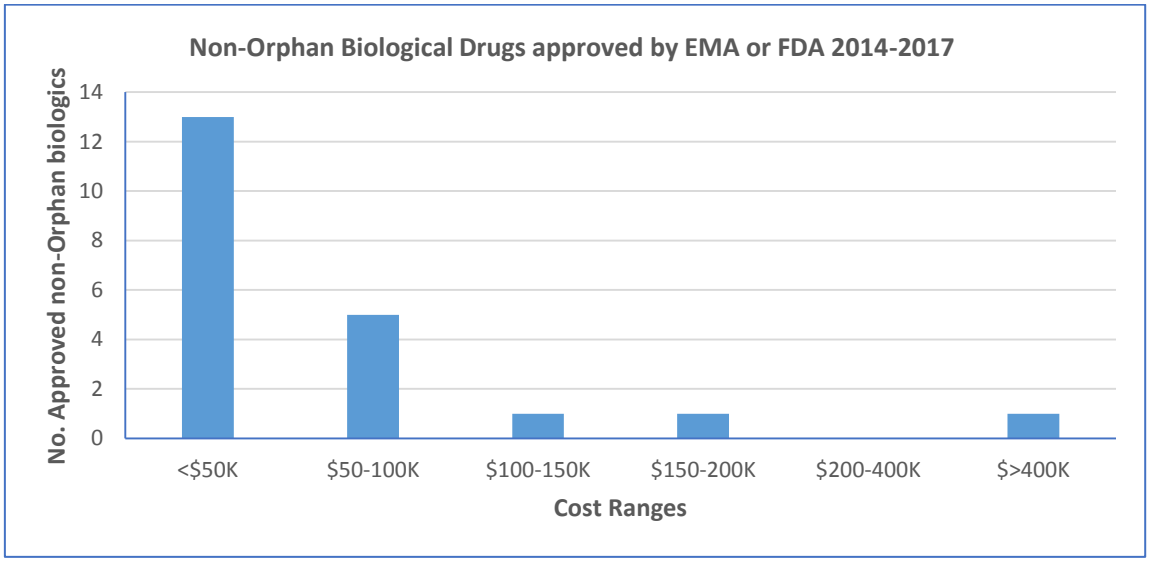

Figure 3.4.4: cost ranges of 21 approved Biologic non-orphan drugs

As can be seen from this data, over 60% of Approved non-Orphan Biologic drugs have a price range of below $50,000, compared to 47% for Chemical Orphan Drugs and 17.5% of Orphan Biologic Drugs.

Less than 15% of Approved non-Orphan Biologic Drugs have a cost range of above $100,000, compared to 35% of Approved Chemical Orphan Drugs and 60% of Approved Biologic Orphan Drugs.

A comparison bar chart of the Cost Ranges of Biologic Orphan and non-Orphan is displayed below:

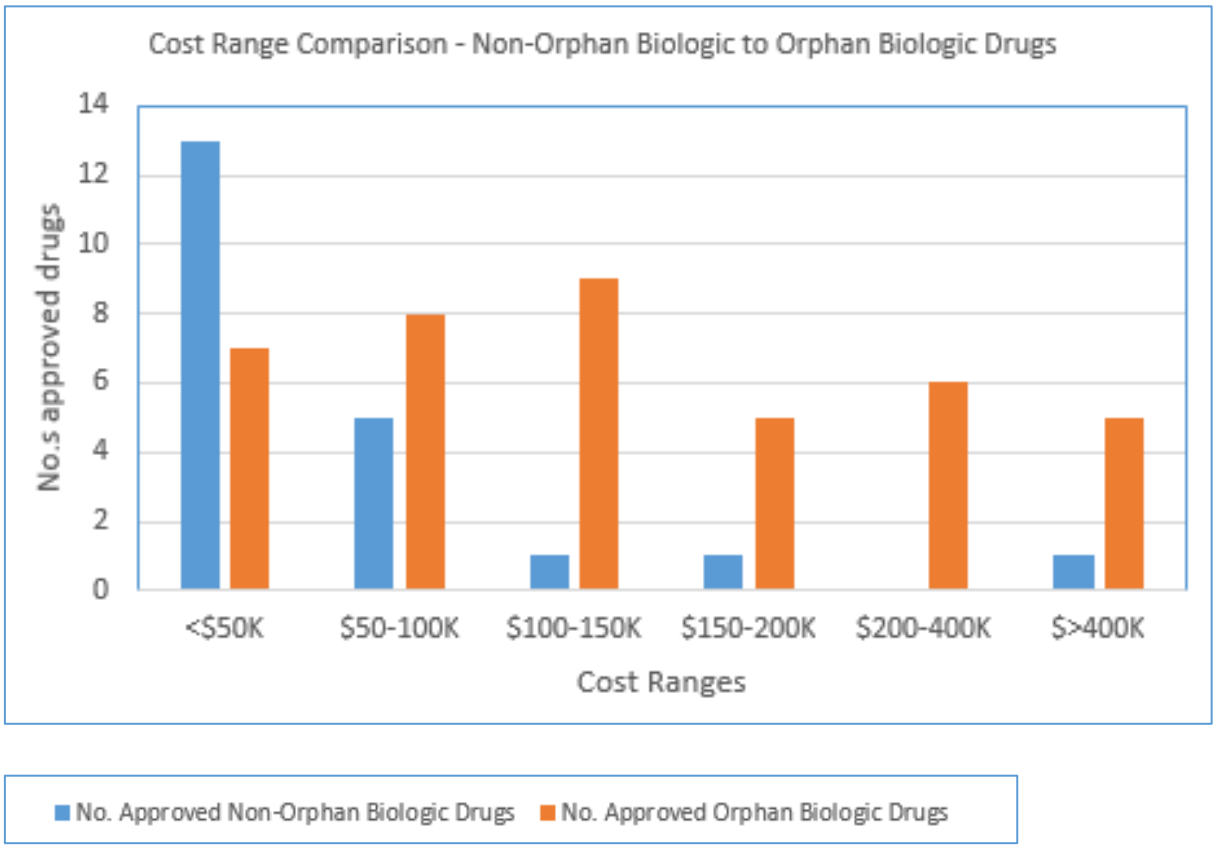

Figure 3.4.5: Comparison of cost ranges of approved biologic Orphan and non-orphan drugs.

Discussion and Results

This high level review of the cost ranges of a number of different categories of drugs agrees with the trend found in the Literature Review for Orphan Drugs in general – that drug pricing is very high for Biologic Orphan Drugs (Capital, n.d.) (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules to Create Prized Monopolies, 2017).

The fact that the cost ranges for Biologic Orphan Drugs exceeds those of Chemical Orphan Drugs may point towards the well-documented costly investment required in Biologic Drug research and development, especially when the risk is greater for Orphan Drugs than for non-Orphan Drugs, considering the much smaller patient cohort group being targeted.

However, when compared to the cost ranges for Biologic non-Orphan Drugs, the cost price for many Biologic Orphan Drugs is still very high, as can be seen in the table above.

Obviously, some specialty biologic drugs will have excessively high costs associated with them, due to the specialist nature of the biotechnology involved, like products comprising of cell fractions, blood plasma products, gene therapy drugs and other products which may have to be specifically tailored to suit individual patients. A case in point is Glybera, a gene therapy treatment marketed by UniQure Biopharma BV. This drug was authorized in 2012 by the EMA to treat hyperproteinemia Type 1. Because of the lack of patients requiring this drug, it was withdrawn from market in October 2017 (refer to EMA website and Glybera authorisations page). This highlights the risk that this company took in investing and bringing to market this very expensive gene therapy drug treatment.

Many of the biologic Orphan drugs with high cost ranges are not specialist biotechnology products, such as Cyramaza (a monoclonal antibody), Vimizim (a biologic) and Keytruda (a monoclonal antibody). All of these drugs cost in excess of $140,000 per patient per year.

These Orphan Drugs also have a 7- to 10-year exclusivity on the market and other drugs cannot be approved to compete with them in this timeframe (FDA, Orphan Drug Act - Relevant Excerpts, 2013) (Hoffmann, 2018)**.**

So the question arises, why are these drugs such a high cost to the patient and should or could they be reduced by the manufacturing companies? Scott Gottlieb, Commissioner of the FDA, has been reported as saying that the high cost of Orphan Drugs is a concern for public health (Tribble, FDA Commissioner: Are The Incentives Right For Orphan Drugs?, 2017). It is difficult to conjecture if drug prices are too high, due to the high level of complexity involved – such as

the cost of drug discovery and development, the high risks involved especially for Orphan Drugs, the high cost of science and technology to manufacture biological drugs, the complexities involved in drug characterization and validation and the potential small market of Orphan Drugs. In addition, the FDA must look at the thousands of rare diseases which don't currently have treatment options which is a large public health concern.

Most, if not all, of the cost of these Orphan Drugs to the patient is borne by either government health departments or health insurance companies (Grant, 2017) and (Simoens, Pricing and reimbursement of orphan drugs: the need for more transparency, 2011). This is where there is likely to be resistance in the future to paying such high prices for drug treatments.

However, this must also be balanced against the fact that most of these drugs provide life-saving options for the patients and are very necessary to address public health issues. Without biopharmaceutical companies investing and taking the risk in bringing the drugs to market, no treatment options would be available.

In the future, biosimilars for these drugs may become available at much reduced cost and this will help bring down the cost ranges for many of these products (Hoffmann, 2018). Developments in technology, such as 3D bioprinting and nanoparticles for drug delivery options, may also help bring down the cost in drug manufacture (Challener, 2016), (Hare, et al., Challenges and strategies in anti-cancer nanomedicine development: An industry perspective., 2017) and (Ozbolat & Hospodiuk, Current advances and future perspectives in extrusion-based bioprinting, 2015). These developments must be welcomed and promoted by the drug regulatory authorities to facilitate a decrease in Biological Orphan Drug costs and as a source of innovation for future drug development for the many patients suffering from untreated rare diseases.

Section 3.5 – Case Studies

Four case studies of selected Orphan Drugs was carried out as part of this project:

3.5.1 Case Study 1 - Keytruda (Pembrolizumab)

Keytruda was selected for this Case Study for a number of reasons. It was the first monoclonal antibody in the list of top selling Orphan Drugs from the Evaluate Pharma Orphan Drug Report 2017 (Pharma E. , Orphan Drug Report 2017, 2017). Keytruda is approved as an Orphan Drug in the US but does not have Orphan Drug status in the EU. Keytruda is a high cost Orphan Drug, with reports of its cost being up to €140,000 per patient in Ireland (Russell, 2017). Keytruda is manufactured by Merck Sharpe and Dohme in Ireland, in its new Carlow biologics facility (Stanton, 2015).

Keytruda FDA Approval

Keytruda is an Orphan monoclonal antibody drug first approved by the FDA in Sept 2014 for the treatment of some types of cancer (unresectable or metastatic melanoma) (reference Keytruda approval page on the FDA website).

Further indications were added to Keytruda by the FDA, namely:

- Sept 2017 - This Prior Approval Supplemental Biologics Application adds a new indication for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy.
- May 2017 - This Prior Approval Supplemental Biologics Application adds a new indication for the treatment of adult and pediatric patients with: unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid

tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

- May 2017 - This Prior Approval Supplemental Biologics Application adds a new indication for the use of pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
- May 2017 - This Prior Approval Supplemental Biologics Application adds a new indication for the use of pembrolizumab, in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer.
- March 2017 - This Prior Approval Supplemental Biologics Application provides for a new indication for the treatment of adult and pediatric patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy.
- August 2016 - This Prior Approval Supplemental Biologics Application adds a new indication for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.
- October 2015 - This Prior Approval Supplemental Biologics Application adds a new indication for the treatment of patients with metastatic, PD-L1 positive, non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.

Keytruda EMA Approval

Keytruda was approved by the EMA in July 2015, but as a standard drug, not as an Orphan Drug (for the treatment of Carcinoma, non-small cell lung cancer, Hodgkin Disease and melanoma).

On 20 July 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the Marketing Authorisation for the

medicinal product Keytruda. The CHMP adopted a new indication as follows: "*Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.*"

In November 2017, MSD withdrew the application for a change to the MA for Keytruda to extend the use of this product in the treatment of non-small cell lung cancer (NSCLC) due to concerns expressed by CHMP about the limited number of patients in the clinical trials.

Keytruda is manufactured by Merck, Sharpe and Dohme Ltd, a large pharmaceutical/ biopharmaceutical company at its biologics facility in Co. Carlow, Ireland.

Cost of Keytruda and expected revenue

Merck indicated Keytruda (pembrolizumab) would cost $12,500 per patient per month, or $150,000 per year. (Weintraub, 2014).

Analysts expected the drug to generate about $1.5 billion in sales for Merck in 2016 and $7.9bn in 2022 (Pharma E. , Orphan Drug Report 2017, 2017).

Keytruda Effectiveness

There have been some comparisons (Lowe, 2016) between the use and effectiveness of Merck's Keytruda and BMS's Opdivo (a non-orphan monoclonal antibody drug) for the treatment of the same condition, a type of lung cancer. Opdivo had sales of double that of Keytruda in 2016 (Pharma E. , Orphan Drug Report 2017, 2017). Presentations on both cancer treatment options were given at a European Society of Medical Oncology conference (Lowe, 2016). The conclusion was that Merck's Keytruda was superior as a treatment for some types of lung cancers (Lowe, 2016). The results from clinical trials for a small cohort of newly diagnosed lung cancer patients was more positive when treated with Keytruda using a specific biomarker to target the diseases (Lowe, 2016). The clinical trial results of Opdivo, in which a broad selection

of lung cancer patients was selected, was not as successful. Price comparisons for both drugs have shown them to be similar, approx. $13,000 per month (Beasley, 2017).

Even though Keytruda has an Orphan Drug status in the US, it has now obtained approval for multiple indications in the US, far exceeding the patient number limit set by the FDA's Orphan Drug Act of 200,000 patients max for orphan drug designation. Keytruda appears to be a very successful drug, offering superior treatment for patients (Lowe, 2016).

These are contributory factors in the high revenue expected from Keytruda sales in the coming years, in addition to the Orphan Drug status 7-years marketing exclusivity period for this drug and the grants and fee waivers offered by the FDA for all Orphan Designated drugs.

Keytruda is on track to be one of the most successful biologic orphan drugs on the market in the coming years. However, there are some recent concerns around the results of some clinical trials for new indications for the drug, where there were patient fatalities during multiple myeloma studies. The FDA has placed a hold on some of these studies (Helfand, 2017).

The National Centre for Pharmacoeconomics in Ireland (NCPE) found pembrolizumab (Keytruda) to be Cost Effective relative to a rival drug Yervoy (ipilimumab) and recommended its use for patients with unresectable or metastatic melanoma in adult patients.

3.5.2 Case Study 2 - Darzalex

Darzalex (daratumumab) is a monoclonal antibody approved by the FDA in Nov 2015 and by the EMA in 2016. It has Orphan Drug designation in both jurisdictions. Darzalex is manufactured by Janssen-Cilag, a subsidiary of the Johnson & Johnson group of companies. It is manufactured in its Cork Janssen Biologics facility (Report E. A., 2016).

It is approved to treat multiple myeloma in the US and the EU.

According to the 2017 Evaluate Pharma Report on Orphan Drugs (Pharma E. , Orphan Drug Report 2017, 2017), Darzalex is set to become the 4th best-selling Orphan Drug in the world by 2022. It is projected to be the second biggest selling orphan monoclonal antibody by 2022 with sales expected to be in the region of $5.8bn in this year. (Pharma E. , Orphan Drug Report 2017, 2017).

FDA Approval: The original approved indication for Darzalex in the US in Nov 2015 was as follows:

- Treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulato1y agent or are double refracto1y to a proteasome inhibitor and an immunomodulato1y agent.

The FDA has extended the indications for Darzalex 3 times in 2016 and 2017, as follows:

- In Nov 2016, the FDA granted a new indication for Darzalex, in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- In Nov 2016, the FDA granted a new indication for Darzalex in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- In June 2017, the FDA granted a new indication for Darzalex in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

MSc (Biopharmaceutical Science) from the Institute of Technology, Sligo

by Denise McDonald, 2018

EMA Approval: The EMA granted a conditional approval to Darzalex for the following indication: treatment of relapsed and refractory multiple myeloma.

In February 2017, the CHMP adopted an extension to the existing indication as follows:

- Darzalex is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Further clinical trials are ongoing with Darzalex and there is some promising news for patients with multiple myeloma, where the studies show improved survival rates and overall response rates, when Darzalex is combined with a new regimen for treatment (McKee, 2017).

Darzalex is the first monoclonal antibody approved for the treatment of multiple myeloma (Staff T. M., 2017). This report suggests that the cost per infusion per patient will be approx. $5850 for an 80-kg patient, amounting to a cost of over $23,000 for the first two months of treatment with this product for the average patient.

In March 2017, the NCPE (National Centre for Pharmacoeconomics in Ireland) carried out a Cost-Effectiveness Assessment of Darzalex at the request of the HSE. It concluded that Darzalex was not cost-effective for the treatment of adult patients with relapsed and refactory Multiple Myeloma and was therefore not recommended for reimbursement by the Health Safety Executive in Ireland (NCPE, 2017). The estimated annual cost of Darzalex was calculated to be twice that of a competitor drug, pomalidomide, and thus not cost-effective.

In October 2017, Genmab (the company which discovered Darzalex and which licenses the product to J&J for manufacture and commercialization), announced profits of $317m for 3rd quarter sales on Darzalex (Genmab, Genmab Announces Net Sales of DARZALEX® (daratumumab) for Third Quarter of 2017, 2017).

3.5.3 Case Study 3 – Strimvelis

Strimvelis, a Gene Therapy Biological Orphan Drug, was selected as a Case Study because of the small number of patients expected to be treated with this product. Also, it is one of the most expensive drugs in the world.

Strimvelis is a medicine used to treat severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), a condition also known as 'Bubble Boy Disease' (Paton, 2018). ADA-SCID is a rare inherited condition in which there is a mutation in the gene which makes adenosine deaminase (ADA), an enzyme essential for maintaining healthy lymphocytes (white blood cells that fight off infections). Without treatment, babies may not survive more than 2 years (Strimvelis, 2016).

Strimvelis treatment involves "*ex vivo*" gene therapy at a treatment centre in Milan, Italy. The patient's bone marrow cells are removed and modified in a laboratory with an engineered virus that contains the functioning ADA gene (Mullin, A Year After Approval, Gene-Therapy Cure Gets Its First Customer, 2017). The newly modified bone marrow cells can then be returned to the patient using a drip into a vein (Mullin, A Year After Approval, Gene-Therapy Cure Gets Its First Customer, 2017). Strimvelis is only the second gene therapy treatment for an inherited condition to be approved across the world (Mullin, A Year After Approval, Gene-Therapy Cure Gets Its First Customer, 2017).

Strimvelis was approved by the EMA in May 2016. It is not yet approved by the FDA but it has been reported that the plan is to seek FDA approval (Adams, 2016).

Strimvelis was developed and manufactured by GSK. It is one of the most expensive drugs ever marketed, with a cost price of over $660,000 for treatment (Staton, 2016) but the company was offering the patients a money-back guarantee if the treatment didn't work. It has not been revealed how the treatment was paid for (Mullin, A Year After Approval, Gene-Therapy Cure Gets Its First Customer, 2017).

The number of patients seeking treatment with Strimvelis is very low, with the company stating that only 8 patients per year are expected. It was reported in 2017 (Mullin, A Year After

Approval, Gene-therapy cure gets its first customer, 2017) that Strimvelis had treated the first patient, a child, with more patients expected this year. A further 4 patients have since been treated (Paton, 2018).

Strimvelis is a specialist biological drug which requires highly specialised techniques tailored to each patient. This type of technology is extremely expensive and is the reason why drugs like this cost so much to produce. The return on investment is likely to be low given the extreme rarity of the indication and the high cost of the research and development required to get the drug to the approval stage.

Strimvelis has not yet been reviewed by the NCPE in Ireland, probably due to the rarity of patients with this condition.

3.5.4 Case Study 4 – Vimizim

Vimizim was selected as a Case Study as it is an Enzyme Replacement Therapy Orphan Biological Drug manufactured by a medium sized company, BioMarin, at its facility in County Cork.

Vimizim contains the active ingredient elosulfase alfa, an enzyme which is used in Enzyme Replacement Therapy for the treatment of an inherited condition, mucopolysaccharidosis type IVA (MPS IVA, also known as Morquio A syndrome) (BioMarin, 2018). The naturally occurring enzyme N-acetylgalactosamine-6-sulfatase works to break down glycosaminoglycans (GAGs) in the body. If it is not present, the level of GAGs starts to rise, causing significant impacts on the patients, such as difficulty moving and breathing, shorter bones and hearing and vision impairment (refer to Vimizim EPAR for details). Vimizin acts as an enzyme replacement for the missing enzyme in the body (BioMarin, 2018).

The occurrence of Morquio syndrome occurs in about 1 in 5000 births (NORD, 2016) so the disease is very rare and many children are affected by it (NORD, 2016).

Vimizim was authorized by the EMA in April 2014. No further indications have been added to its label by the EMA.

Vimizin was approved by the FDA in February 2014. No further indications have been added to its label by the FDA.

Vimizim is one of the most expensive medicines, with a cost of up to $380,000 per patient expected (Young D. , 2014).

The NCPE has found Vimizim to be not cost effective as the treatment would last for a patient's lifetime and it was difficult to determine which patient would respond to treatment and which would not. Also, there were some concerns over the lack of clinical evidence to support treatment over the patient's lifetime. Therefore, reimbursement for this drug was not recommended.

A study in 2017 found that Vimizim, when being used as a long-term treatment for the Morquio A condition is effective for patients (Radke, 2017).

CHAPTER 4 - OVERALL CONCLUSIONS AND RECOMMENDATIONS

Orphan Drugs serve a critical area of the public healthcare system, where they address the needs of severely ill patients, who suffer from rare diseases, for which there is often no other treatment option available (FDA, Orphan Drug Act - Relevant Excerpts, 2013). Because of the wide number of rare diseases across the world, there is a major need for large numbers of Orphan Drugs to treat these diseases. From carrying out this project, it is apparent that this need can only be addressed by the efforts of large multi-national pharmaceutical and biopharmaceutical companies, sometimes working in collaboration with smaller specialty biotech companies. Together, they have the resources and expertise to research and develop new drugs or to re-purpose existing drugs, many of them biological in nature, to address this gap.

Trends show that, while still quite low, there are increasing numbers of Biological Orphan Drugs being approved by the FDA and EMA regulatory authorities in recent years. These drugs are treating rare and sometimes fatal diseases, many of which have been untreated before, drugs such as Besponsa (which treats certain types of Acute Lymphoblastic Leukaemia), Bavencio (used for treating neuroendocrine tumors) and Darzalex (used to treat cancer of the bone marrow in adults). This trend is a very welcome development for sufferers of these conditions.

In this regard, it can be strongly argued that the investment of manufacturing companies in new drug discovery and development is meeting the needs identified by the Orphan Drug Act (ODA), which was first enacted in 1983 in the US. The driver of this Act was to stimulate industry interest in developing new drugs for rare diseases, which up until then was not addressing the public health needs at the time. Thus, every new Orphan Drug approved by the authorities is to be welcomed as a further effort in fighting deadly diseases.

The future of the ODA must be preserved and enhanced to secure more industry interest in this area of drug manufacturing. This interest and investment in drug discovery for rare diseases cannot be taken for granted, as there are examples where even if a drug gets approval for a rare disease, it may still not be a marketing success for the manufacturing company and the investment by the company is lost. Glybera is a case where the approved drug was withdrawn by the manufacturing company due to its failure in the marketplace. Cautionary experiences such as

this may impact future investment in the area. The risk of an Orphan Designated Drug either failing to get regulatory approval or failing in the market place is high and can result in major financial losses for companies.

The numbers of biological Orphan Drugs getting approval in the EMA and the FDA continues to be low overall, with the average numbers over the past eight years being 2.2 and 3.5 drug approvals, respectively (reference Table 3.1.9 in this report). In comparison, the average numbers of Chemical Orphan Drugs gaining approval over the past ten years are 6.7 and 13.7 drug approvals, respectively. However, the numbers of Biological Orphan Drugs getting approval does show a slight increase in recent years and there is much industry interest in Orphan Drug discovery and development, so the future for the Orphan Drug industry does seem to be positive.

The numbers of Biological Orphan Drugs getting approval in the US and the EU are comparable, with generally higher numbers in the US – this was observed in the Project Literature Review Chapter (Section 3.2 Recent Trends in Orphan Drug Approval) and subsequently confirmed in the Results Chapter for Biological Orphan Drugs (Section 3.1). This could be due to regulatory differences between the two regions as the drugs are being approved in the EU but as standard drugs, not as Orphan Drugs. In addition, there may be a higher focus on Orphan Drug development in the US than in the EU or there may be smaller numbers of patients of particular diseases in the US than in the EU.

Many of the companies involved in the manufacturing of Biological Orphan Drugs are large multi-national companies, a trend observed in the Literature Review Chapter for Orphan Drugs and confirmed in the Results Chapter for Biological Orphan Drugs. Some of these companies have partnered with or acquired the smaller companies which initially discovered the Orphan Drug (Bioworld, 2016), (Protalix, 2018) (Sherry Ku M. , 2015). There is space in the industry for the involvement of small biotech companies in the highly technical environment of specialist biological drug discovery, where new innovations are the norm, rather than the exception. However, in order to successfully globally market biological drugs, it may be necessary to

partner with the larger pharmaceutical companies close to the final regulatory approval stage (Bioworld, 2016), (Protalix, 2018) (Sherry Ku M. , 2015).

From the Literature Review and Results Chapters of this project, it does appear that there are some differences in the way drugs are awarded Orphan Drug designation during their development process and in the incentives offered to companies to invest in this area of drug development between the EMA and the FDA. More drugs get Orphan Drug Designation in the US than in the EU and more Orphan Designated drugs get approval in the US than in the EU. This may incentivize some companies to target the US for Orphan Drug Designation and approval ahead of the EU, which seems to be the case for many of the drugs reviewed for this project (Brennan, 2018).

This may mean that some approved drugs which have Orphan Drug status in the US but not in the EU will get the incentives and market exclusivity awarded in the US but not in the EU. Some biological Orphan Drug examples which have Orphan Drug status in the US but not in the EU include Keytruda, Portrazza and Repatha. This disparity occurs despite the existence of a joint working group in Orphan Drug Designations and Approvals between the EMA and the FDA. This may result in some companies viewing the US as an easier path to getting their drug Orphan Designation than in the EU and as such, it may be the more viable route to getting the drug approved initially.

In order to have a more streamlined and transparent process for Orphan Drug Designation, review and approval, and to expedite the process, closer cooperation and alignment between the two regulatory working groups in this area is a recommendation of this project.

From carrying out this project, there is no doubt that Orphan Drugs, and in particular Biological Orphan Drugs, have become a major business opportunity for many pharmaceutical companies and a key focus area for regulatory authorities, with up to 40% of new drugs being approved in the EU and the US having the Orphan Drug status. It does seem that many companies are

actively targeting the Orphan Drug Designation for their biological products or the acquisition of drugs with Orphan Drug Designation. It is difficult to be definitive about the reasons for the increasing interest in Biological Orphan Drugs in recent years but there can be no doubt that the return on investment on these drugs must be a major driver in this trend (Pagliarulo, 2017).

Indications from the Project Literature Review do indicate that the revenue generated from Orphan Drugs, and in particular Biological Orphan Drugs, is becoming a substantial part of the overall revenue for large biopharmaceutical companies, with increasing sales predicted over the next 5 years (Pharma E. , Orphan Drug Report 2017, 2017). Clearly, the incentives offered by the regulatory authorities for companies to target their R&D efforts on Orphan Drugs is proving very attractive to many companies, in particular the 7- to 10-years market exclusivity. This extensive market exclusivity can provide a valuable return on investment for a company's efforts in drug discovery and development and facilitate valuable future drug discovery work (Fagnan, Gromatzky, Stein, Fernandez, & Lo, 2014).

From the Project Literature Review and the Results Chapter of this project, the cost of some Biologic Orphan Drugs to the patient does seem to be extremely high and out of the reach of some patients who may need the drug treatment. Orphan Drug treatments which cost in excess of $50-100,000 per patient per year are out of the reach of many of patients and of government and health insurance companies who fund many medical treatments. Yet, as the Results Chapter shows, the cost of the majority (>60%) of biological Orphan Drugs are in excess of $100,000 per patient per year, with some (over 27%) having a cost range of above $200,000 per patient per year.

The Results Chapter of the project compared the price range of different drug categories and showed that Biological Orphan Drugs have a much higher price range than either Chemical Orphan Drugs or Biological non-Orphan Drugs. The reasons for this are not clear. The Orphan nature of the drug may mean the target number of patients is smaller than for standard drugs. However, this is the case with Chemical Orphan Drugs also, which have a much lower drug price range than Biological Orphan Drugs. The biological nature of the drugs can lead to higher drug discovery and development costs but this cannot be the main cause of the high drug prices

as Biological non-Orphan Drugs, while having quite high drug costs also, are not in the same high drug price range as Biological Orphan Drugs. Some Biological Orphan Drugs may have similar or higher numbers of patients being treated as some Biological non-Orphan Drugs so the return on investment will be similar or higher.

Clearly, some balance is required between Biological Orphan Drug cost to the patient and the return on investment to the developing company, so that patients get the treatment they need at a reasonable cost and the companies get a return on investment for their shareholders and funds to enable future Orphan Drug discovery and the continued innovation that is required in the industry. It is a recommendation of this project that this balance should be promoted by the regulatory authorities and governments of the regions.

A further recommendation of this project is that there must be a driver for self-regulation in relation to product cost within the industry itself, similar to the way that GMP and product quality have become significantly self-regulated by the large pharmaceutical companies, driven by GMP regulations and quality inspections (Schmitt, 2015) and (WHO, 2011).

Another recommendation from this project is that closer cooperation between the FDA and the EMA in terms of drug pricing between the regions is a necessity. Closer cooperation and alignment between different countries within the EU should also be a goal, as the Project Literature Review indicates there may be disparities in product cost between different EU countries, which should be addressed.

Finally, a recommendation from this project in the area of the Orphan Drug Act would be a review of the periods of exclusivity which are awarded to Approved Orphan Drugs. This timeline could be reduced if Orphan Drugs obtain additional indications. These additional indications could provide the necessary revenue for the marketing company for further research and development, meaning that there would be no requirement for the long period of market exclusivity for the original Orphan indication.

One area of biological drug development which may provide some answers to these drug-pricing problems in the future is the area of biosimilars. Biosimilars are those biological drugs which are very similar in structure and function to the original proprietary product without necessarily being identical and manufactured generally by a different company (FDA, Biosimilar and Interchangeable Products, 2017). They may not have the same high cost as the original drug, as the manufacturers of biosimilars will not have the drug discovery and development cost to address in drug pricing. Biosimilars were outside the scope of this project but it is recommended that the range and applicability of biosimilars for rare diseases be improved, as biosimilars may provide the leverage necessary to force a reduction in the cost of some biological Orphan Drugs to the patient (AHIP, 2018).

Another area of biological drugs which may help with reducing overall Orphan Drug pricing in the future is Gene Therapy. Developments in a Gene Therapy treatment for the rare disease Spinal Muscular Atrophy (SMA) Type I and 2 by AveXis, a clinical stage gene therapy company, are promising and if successful could result in a single-treatment option for the disease (AveXis, 2017). This could result in a huge price reduction on the only recently-approved current treatment option of Spinraza, which costs up to $750,000 per patient per year (Smith, 2017). Further developments in single-treatment gene therapy drugs may provide hope for other sufferers of rare genetic diseases (Radcliffe, 2018).

One area of weakness in this research is the difficulty in obtaining accurate Biological Orphan Drug prices and the complexities involved in determining accurate drug discovery and development costs for the companies. This project relied heavily on media and journal articles for drug pricing information, which may not have access to the most accurate drug pricing information and the differences which may exist in different countries.

High drug costs make good headlines for media articles but may not reflect the actual drug cost to the patient. More accurate information would have to be obtained from medical and health insurance companies and government bodies. Attempts were made to obtain drug prices from Irish Health Insurance companies but this information is considered commercially sensitive and is not disclosed to third parties. Attempts were also made to obtain drug cost data from national

websites such as MIMS.co.uk and the Common European Drug Database (//cedd.oep.hu) but no information on Orphan Drug pricing specifically could be determined.

As outlined in the Results Chapter, many Biological Orphan Drugs have been granted more than just one indication for patient treatment. This extension of indications can happen within a couple of years after the initial approval for the Orphan Indication, as was the case for Darzalex, Xiaflex and Cyramaza. If the additional extensions are granted for orphan indications, this can extend the market exclusivity period for Orphan Drugs significantly and ensure further return on investment for the product. This may be an attractive option of many companies to pursue and can be positive sign for future investment and growth in the industry.

In the Project Literature Review Chapter, regulatory approval timelines were reviewed for Orphan Drugs. It was found that regulatory pathways can be shorter for Orphan Drugs (Sherry Ku, 2005) but clinical trials may need to be broader in scope (more global) due to much smaller patient numbers. There was no observed difference in clinical trial requirements for Orphan Drugs, even though the regulatory approval process for this drug category may be expedited. Having expedited regulatory approval pathways is not practical for all drugs so priority must be given to Orphan Drugs which have potential to save patients' lives.

Conclusions

The research conducted in this area does seem to show much media interest and focus on Biological Orphan Drugs, with much research being carried out on this topic. This follows the growing industry interest in Orphan Drugs in recent years. Many of the media articles focus on the cost of these drugs to patients, which is understandable. However, there did not seem to be as much focus on the costs involved in Orphan Drug development, especially of biological drugs and the risks that companies take when deciding to bring an Orphan Drug through the drug development process. A risk that for some companies may not pay off, and can lead large revenue losses as a result. All of these drug development costs must be compensated for in the cost of successful Orphan Drugs.

In addition, there should be more focus in the media in driving further collaboration between the different regulatory agencies and between the Regulators and the industry in terms of Orphan Drug approvals and drug pricing. This is especially true given the disparity observed between drugs given Orphan Drug status in the US but not in the EU and the different price structures which exist in different countries.

Given the very high cost of the majority of Biological Orphan Drugs, there is an ethical issue of access of patients to these potentially life-saving treatments. Can the high prices be justified in these cases? Can life-saving drugs be sold on the global market as if they were regular commodities without price regulation? These questions must be considered when granting Orphan Drug approval for new drugs.

Support is required from the regulators and health authorities in both regions for the developments of biosimilars and other types of lower-cost medications which can provide an alternate for existing high-cost Orphan Drugs and for new innovations and biotechnologies which can help lower the cost of new drugs.

From carrying out this project, it is clear that further Orphan Drug discovery is required to address the high numbers of rare diseases for which there is no current treatment. Thus, FDA and EMA incentives must continue to entice smaller and medium size enterprises and institutes to research and develop new drugs for these diseases.

Recommendations

Further research is required in this area of Biological Orphan Drugs, with a focus on the following:

- More accurate cost pricing models,
- The impact on cost of biosimilars and whether biosimilars are the future of drugs for rare diseases,
- Whether smaller companies are still involved in research and development of Orphan Biologic Drugs etc.

CHAPTER 5 – APPENDICES

SECTION 5.1 APPENDIX 1

Listing of Orphan Drugs Approved by the EMA and the FDA Regulatory Authorities in years 2010-2015.

EMA Authorisations

2015

Name of Drug	Active Substance	Approved Indication	Type of drug	MAH
Blincyto	Blinatumomab	Precursor Cell Lymphoblastic Leukemia-Lymphoma	mAb	Amgen
Kanuma	sebelipase alfa	Lipid Metabolism, Inborn Errors	Biologic	Alexion
Strensiq	asfotase alfa	Hypophosphatasia	Biologic	Alexion
Holoclar	*ex vivo* expanded autologous human corneal epithelial cells	Corneal Diseases	Biologic	Chiesi Farmaceutici spa

Table 5.1: Orphan Biological Drugs approved by the EMA in 2015.

Type of Orphan Drug	Number
Chemical	10
Monoclonal Antibody	1
Biological, but not mAbs	3

Table 5.2: Summary of Orphan Drugs approved by the EMA in 2015.

The 10 Chemical Orphan Drugs approved by the EMA in 2015 are Raxone, Ravicti, Ofev, Kyprolis, Cholbam, Cresemba, Cerdelga, Lenvima, Hetlioz and Farydak.

2014

Name of Drug	Active Substance	Approved Indication	Type of drug	MAH
Gazyvaro	Obinutuzumab	Leukaemia	mAb	Roche Registration Ltd
Sylvant	Siltuximab	Giant lymph node hyperplasia	mAb	Janssen-Cilag International
Vimizim	recombinant human n-acetylgalactosamine-6-sulfatase (rhgalns)	Mucopolysaccharidosis IV	Biologic	Biomarin

Table 5.3: Orphan Biological Drugs approved by the EMA in 2014.

Type of Orphan Drug	Number
Chemical	10
Monoclonal Antibody	2
Biological, but not mAbs	1

Table 5.4: Summary of Orphan Drugs approved by the EMA in 2014.

The 10 Chemical Orphan Drugs approved by the EMA in 2014 are Adempas, Cometriq, Deltyba, Granupas, Imbruvica, Ketoconazole, Lynparza, Scenesse, Sirturo and Translarna.

2013

No biologic or monoclonal antibody Orphan Drugs were approved by the EMA in 2013.

Type of Orphan Drug	Number
Chemical	6
Monoclonal Antibody	0
Biological, but not mAbs	0

Table 5.5: Summary of Orphan Drugs approved by the EMA in 2013.

The 6 Chemical Orphan Drugs approved by the EMA in 2013 are Procysbi, Orphacol, Opsumit, Imnovid, Iclusig and Bosulf. Defitelio is not included as it is a specialist biological/chemical drug.

2012

Name of Drug	Active Substance	Approved Indication	Type of drug	MAH
Adcetris	Brentuximab vedotin	Hodgkin Lymphoma	mAb	Takeda
Nexobrid	Bromelain - concentrate of proteolytic enzymes	Debridement	Biologic	Mediwound Germany GmbH

Table 5.6: Orphan Biological Drugs approved by the EMA in 2012.

Type of Orphan Drug	Number
Chemical	6
Monoclonal Antibody	1
Biological, but not mAbs	1

Table 5.7: Summary of Orphan Drugs approved by the EMA in 2012.

The 6 Chemical Orphan Drugs approved by the EMA in 2012 are Revestive, Signifor, Xaluprine, Kalydeco, Dacogen and Bronchitol.

2011

No biologic or monoclonal antibody Orphan Drugs were approved by the EMA in 2011.

Type of Orphan Drug	Number
Chemical	5
Monoclonal Antibody	0
Biological, but not mAbs	0

Table 5.8: Orphan Drugs approved by the EMA in 2011.

The 5 Chemical Orphan Drugs approved by the EMA in 2011 are Esbriet, Plenadren, Tobi Podhaler, Votubia and Vyndaqel.

2010

Name of Drug	Active Substance	Approved Indication	Type of drug	MAH
Arzerra	Ofatumumab	Leukemia, Lymphocytic, Chronic, B-Cell	mAb	Novartis
Vpriv	velaglucerase alfa	Gaucher Disease	Biologic	Shire Ireland Pharma

Table 5.9: Detail of Orphan Biological Drugs approved by the EMA in 2010.

Type of Orphan Drug	Number
Chemical	1
Monoclonal Antibody	1
Biological, but not mAbs	1

Table 5.10: Summary of Orphan Drugs approved by the EMA in 2010.

The one Chemical Orphan Drug approved by the EMA in 2010 is Tepadina.

FDA Authorisations

2015

Name of Drug	Active Substance	Approved Indication	Type of drug	Sponsor
Kanuma	sebelipase alfa	Lipid Metabolism, Inborn Errors	Biologic	Alexion
Strensiq	asfotase alfa	Hypophosphatasia	Biologic	Alexion
Unituxin	Dinotuximab	Neuroblastoma	mAb	United Therapeutics
Natpara	Parathyroid hormone	Hypocalcemia	Biologic	NPS Pharma
Portrazza	Necitumumab	Cancer	mAb	Eli Lilly
Darzalex	Daratumumab	Cancer Treatment	mAb	Janssen-Cilag International
Praxbind	Idarucizumab	For patients who take anti-coagulant during emergency situations	mAb	Boehringer Ingelheim
Empliciti	Elotuzumab	Multiple myeloma	mAb	BMS
Repatha	Evolocumab	Familial hyper cholesterolemia	mAb	Amgen

Table 5.11: Orphan Drugs approved by the FDA in 2015.

Type of Orphan Drug	Number
Chemical	20
Monoclonal Antibody	6
Biological, but not mAbs	3

Table 5.12: Summary of Orphan Drugs approved by the FDA in 2015.

The 20 Chemical Orphan Drugs approved by the FDA in 2015 are Yondelis, Orkambi, Cotellic, Xuriden, Tagrisso, Ninlaro, Cholbam, Uptravi, Cresemba, Alecensa, Lenvima, Farydak, Duopa, Phoxilium, Kalydeco, Jadenu, Envarsus, Iressa, Onivyde and Vistogard.

2014

Name of Drug	Active Substance	Approved Indication	Type of drug	Sponsor
Cyramza	Ramucirumab	Advanced gastric cancer	mAb	Eli Lilly
Myalept	Metreleptin	To treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy	Biologic	Aegerion/Amylin Pharma LLC
Keytruda	Pembrolizumab	Patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.	mAb	MSD
Blincyto	Blinatumomab	Precursor Cell Lymphoblastic Leukemia-Lymphoma	mAb	Amgen
Opdivo	Nivolumab	Treatment of patients with unresectable or metastatic melanoma and disease progression	mAb	BMS
Sylvant	Siltuximab	Giant lymph node hyperplasia	mAb	Janssen-Cilag International
Vimizim	recombinant human n-acetyl-galactosamine-6-sulfatase (rhgalns)	Mucopolysaccharidosis IV	Biologic	Biomarin

Table 5.13: Orphan Drugs approved by the FDA in 2014.

Type of Orphan Drug	Number
Chemical	15
Monoclonal Antibody	5
Biological, but not mAbs	2

Table 5.14: Summary of Orphan Drugs approved by the FDA in 2014.

The 15 Chemical Orphan Drugs approved by the FDA in 2014 are Lynparza, Signifor, Ofev, Esbriet, Cerdelga, Zydelig, Ryanodex, Beleodaq, Zykadia, Purixan, Impavido, Hemangeol, Northera, Hetlioz and Decitabine.

2013

Name of Drug	Active Substance	Approved Indication	Type of drug	Sponsor
Gazyvaro	Obinutuzumab	Leukaemia	mAb	Roche Registration Ltd

Table 5.15: Orphan Drugs approved by the FDA in 2013.

Type of Orphan Drug	Number
Chemical	15
Monoclonal Antibody	1
Biological, but not mAbs	0

Table 5.16: Summary of Orphan Drugs approved by the FDA in 2013.

The 15 Chemical Orphan Drugs approved by the FDA in 2013 are Orenitram, Kuvan, Imbruvica, Opsumit, Adempas, Valchlor, Epaned, Gilotrif, Mekinist, Tafinlar, Nymalize, Procysbi, Pomalyst, Ravicti and Kynamro.

2012

Name of Drug	Active Substance	Approved Indication	Type of drug	Sponsor
Voraxaze	Glucarpidase	For the treatment of cancer patients with impaired kidney function	Biologic	BTG International
Raxibacumab	Raxibacumab	Prophylaxis and treatment of inhaled anthrax	mAb	Human Genome Sciences/GSK
Elelyso	taliglucerase alfa	Gaucher Disease	Biologic	Pfizer/Protalix

Table 5.17: Orphan Drugs approved by the FDA in 2012.

Type of Orphan Drug	Number
Chemical	19
Monoclonal Antibody	1
Biological, but not mAbs	2

Table 5.18: Summary of Orphan Drugs approved by the FDA in 2012.

The 19 Chemical Orphan Drugs approved by the FDA in 2012 are Sirturo, Juxtapid, Gattex, Onfi, Iclusig, Signifor, Cometriq, Synbrio, Cystaran, Bosutinib, Revatio, Afinitor, Kyprolis, Korlym, Sodium Thiosulphate, Sodium Nitrite, Mitosol, Kalydeco and Viread.

2011

Name of Drug	Active Substance	Approved Indication	Type of drug	Sponsor
Yervoy	Ipilimumab	Cancer Treatment	mAb	BMS
Nulojix	Belatacept	Graft RejectionKidney Transplantation	Biologic	BMS
Adcetris	Brentuximab vedotin	Hodgkin Lymphoma	mAb	Seattle Genetics
Erwinaze	Asparaginase erwinia chrysantemi	Acute lymphoblastic leukemia, acute myeloid leukemia, and non-Hodgkin's lymphoma	Biologic	Jazz Pharma/EUSA Pharma

Table 5.19: Orphan Drugs approved by the FDA in 2011.

Type of Orphan Drug	Number
Chemical	11
Monoclonal Antibody	2
Biological, but not mAbs	2

Table 5.20: Summary of Orphan Drugs approved by the FDA in 2011.

The 11 Chemical Orphan Drugs approved by the FDA in 2011 are Jakafi, Onfi, Ferriprox, Xalkori, Firazyr, Zelboraf, Phoslyra, Omvocate, Banzel, Makena and Nithiodote.

2010

Name of Drug	Active Substance	Approved Indication	Type of drug	Sponsor
Xiaflex	Clostridial Collagenase	Peyronie's disease	Biologic	Auxilium Pharma
Lumizyme	Alglucosidase Alfa 2	Pompe Disease	Biologic	Genzyme Corp
Krystexxa	Pegloticase	Severe, treatment-refractory, chronic gout	Biologic	Horizon Pharma
Vpriv	Velaglucerase alfa	Gaucher disease	Biologic	Shire Human Genetic Therapies

Table 5.21: Orphan Drugs approved by the FDA in 2010.

Type of Orphan Drug	Number
Chemical	4
Monoclonal Antibody	0
Biological, but not mAbs	4

Table 5.22: Summary of Orphan Drugs approved by the FDA in 2010.

The 4 Chemical Orphan Drugs approved by the FDA in 2010 are Ampyra, Cayston, Carbaglu and Glycopyrrolate Oral Solution.

Some drugs are approved repeatedly for new Orphan Indications.

5.2 APPENDIX 2

Information obtained on size of companies manufacturing biologic and monoclonal antibody Orphan Drugs (approved in either the EU, US or both regions as Orphan Drugs), 2010-2017.

Company Name	Orphan Drugs (type)	No. Products by company	No. Employees in company	Revenue/ Sales in Company	Company Size
Takeda	Adcetris (mAb)	>15 (Pharma T. , Takeda What We do, n.d.)	>6500 (Pharma T. , Takeda Company Information, n.d.)	>16bn (USD) (Pharma T. , Takeda Annual Report 2016, n.d.)	Large
Pfizer	Elelyso (biologic) Besponsa (mAb)	>30 (Pharma P. , Pfizer Company Factsheet, n.d.)	>90,000 (Pharma P. , Forbes Top Regarded Companies, n.d.)	203bn (USD) (Pharma P. , Forbes Top Regarded Companies, n.d.)	Large
Roche/ Genentech	Gazyvaro (mAb) Hemlibra (mAb)	>20 (Pharma R. , Roche Products List, n.d.)	>90,000 (Pharma R. , Roche 2015 Annual Report, n.d.)	>37bn (USD) (Report N. A., n.d.)	Large
MediWound Germany	Nexobrid (biologic)	1 (MediWound, n.d.)	72 (Mediwound, n.d.)	1.5m (USD) (Mediwound, n.d.)	Small
Jazz Pharma Inc	Erwinaze (biologic)	6 (Pharma J. , Jazz Pharma Products, n.d.)	850 (companies, n.d.)	1.5bn (USD) (Pharma J. , Jazz Pharma Annual Report 2016, n.d.)	Large
Janssen-Cilag	Sylvant (mAb) Darzalex (mAb)	>20	>120,000 (Pharma J. , Janssen Products, n.d.)	>71bn (USD) (Pharma J. , Johnson&Johnson	Large

		(Pharma J. , Janssen Products, n.d.)		Annual Report 2016, n.d.)	
BioMarin	Vimizim (biologic) Brineura (biologic)	6 (Pharma B. , n.d.)	2200 (Pharma B. , n.d.)	171m USD (Pharma B. , n.d.)	Medium
Amgen	Blincyto (mAb) Repatha (mAb)	16 (Pharma A. , Amgen Products, n.d.)	>19,000 (Forbes, Forbes - World's Best Employers, n.d.)	23bn (USD) (Pharma A. , Amgen Financial Report 2016, n.d.)	Large
Alexion	Kanuma (biologic) Strensiq (biologic)	3 (Pharma A. , Alexion Products, n.d.)	>2000 (Pharma A. , Alexion Annual Report 2016, n.d.)	>1bn (USD) (Pharma A. , Alexion Annual Report 2016, n.d.)	Large
United Therapeutics	Unituxin (mAb)	5 (Therapeutics, n.d.)	750 (Forbes, Forbes - The World's Biggest Public Companies, n.d.)	5.4bn (USD) (Forbes, Forbes - The World's Biggest Public Companies, n.d.)	Large
Chiesi Farmaceutici spa	Holoclar (biologic)	>11 (group, n.d.)	>4800 (Group, n.d.)	>1.8bn (USD) (Group, n.d.)	Large
Biogen Inc	Alprolix (biologic)	>10 (Inc, Biogen Inc Research Pipeline, n.d.)	>7000 (Forbes, Forbes - Global 2000 Growth Companies, n.d.)	>11bn (USD) (Inc, Biogen Annual Report 2016, n.d.)	Large
Eli Lilly	Lartruvo (mAb) Cyramaza (mAb)	>20 (Pharma E. L., n.d.)	>40,000 (Pharma E. L., n.d.)	>21bn (USD) (Pharma E. L., n.d.)	Large

	Portrazza (mAb)				
GSK	Strimvelis (biologic) Ravibacumab (mAb)	>10 (Pharma G. , GSK Products, n.d.)	<100,000 (Pharma G. , GSK About US, n.d.)	>4bn (USD) (Pharma G. , GSK Annual Report, n.d.)	Large
MolMed spa	Zalmoxis (biologic)	3 (spa, MolMed About , n.d.)	>162 (spa, MolMed Press Release, Page 3)	>20,000 (USD) (spa, MolMed Press Release, Page 3)	Small
Auxilium Pharms	Xiaflex (biologic)	>20 (Pharma A. , n.d.)	>6000 (Forbes, Forbes - The World's Biggest Public Companies, n.d.)	>7bn (USD) (Forbes, Forbes - The World's Biggest Public Companies, n.d.)	Large
Genzyme	Lumizyme (biologic)	>8 (Genzyme, Genzyme Products, n.d.)	>110,000 (Genzyme, Genzyme About Us, n.d.)	>33bn (USD) (Genzyme, Genzyme About Us, n.d.)	Large
Horizon Pharma	Krystexxa (biologic)	10 (Horizon, n.d.)	>1000 (Horizon, n.d.)	>1bn (USD) (Horizon, n.d.)	Large
BMS	Yervoy (mAb) Nulojix (biologic) Opdivo (mAb) Empliciti (mAb)	>8 (Squibb, n.d.)	>27,000 (Squibb, n.d.)	17bn (USD) (Squibb, n.d.)	Large
Seattle Genetics	Adcetris (mAb)	1	>800 (journals, n.d.)	>520m (USD)	Medium

		(Genetics, Seattle Genetics Products, n.d.)		(Genetics, Seattle Genetics Annual Report, n.d.)	
BTG International	Voraxaze (biologic)	>4 (BTG, n.d.)	>1300 (Wire, n.d.)	>2.9bn (USD) (Forbes, Forbes - Most Innovative Growth Companies, n.d.)	Medium
Novelion Therapeutics Inc	Myalept (biologic)	5 (Novelion T. I., Novelion Therapeutics Products Pipeline, n.d.)	>163 (Bloomberg, n.d.)	>50m (USD) (Novelion T. I., Novelion Therapeutics Preliminary 2016 report, n.d.)	Medium
Merck Sharpe & Dohme	Keytruda (mAb)	>20 (MSD, n.d.)	>60,000 (Merck, n.d.)	>39bn (USD) (Merck, n.d.)	Large
EMD Serono Inc	Bavencio (mAb)	>7 (Serono, n.d.)	>38000 (EMD S. , n.d.)	>11bn (USD) (EMD S. , n.d.)	Large
Boehringer Ingelheim International	Praxbind (mAb)	>20 (Ingelheim, n.d.)	>50,000 (Ingelheim, n.d.)	>15bn (USD) (Ingelheim, n.d.)	Large
Elusys Therapeutics Inc	Anthim (mAB)	1 (Elusys, n.d.)	N/A	>16m (USD) (Elusys, n.d.)	Small
Ultragenyx Pharma	Mepsivii (biologic)	7 (Ultragenyx, Ultragenyx Pipeline, n.d.)	376 (WSJ, n.d.)	>100,000 (USD) (Ultragenyx, Ultragenyx 2016 Financial Results, n.d.)	Small

Table 5.23: Details of companies manufacturing biological Orphan Drugs.

5.3 APPENDIX 3

Summary of data obtained on extension of indication for Biologic and Monoclonal Antibody Orphan Drugs approved by the FDA and/or the EMA, 2010-2017.

Drug	Drug Sponsor	Detail on Extension (or refusal) of marketing authorisation
Keytruda	MSD – originally approved by the FDA in Aug 2014.	The FDA granted extensions of indications for Keytruda in May and Sept 2017 (FDA, FDA Approved Drug Products for all products, 2017).
Arzerra	Novartis – originally approved by the FDA in Oct 2009.	The FDA approved extensions for the indication of Arzerra in 2014 and 2016 (FDA, FDA Approved Drug Products for all products, 2017). The EMA also approved an extension of indication for Arzerra in 2017 and 2016 (refer to Assessment History for this drug on the EMA website).
Blincyto	Amgen – originally approved by the FDA in 2014.	A supplemental Biologics Applications License has been submitted to the FDA for extensions of indications for Blincyto in Feb 2017 (Broderick, 2017).
Lartruvo	Eli Lilly – originally approved by the FDA in 2016.	Phase II and Phase III trials are in progress in an attempt to extend the indication for Lartruvo to other types of cancers (Shirley, 2016).
Myalept	Novelion Therapeutics – originally approved by the FDA in 2014.	This drug is in Phase III trials to extend its indication (Novelion W. , 2017).

Bavencio	EMD Serono – originally approved by the FDA in March 2017.	Bavencio is in Phase I, II and III trials to extend its indications (EMD W. , 2017).
Repatha	Amgen Inc – originally approved by the FDA in 2015.	Received approval for new indications for a much broader population base (FDA, FDA Approved Drug Products for all products, 2017) and (Tribble & Lupkin, Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies, 2017).
Adcetris	Seattle Genetics – originally approved by the FDA in 2011.	The FDA approved extensions for the indications of Adcetris in 2015 and 2017 (FDA, FDA Approved Drug Products for all products, 2017). Extension of indication was also approved by the EMA in 2016 (refer to Assessment History for this drug on EMA website).
Lumizyme	Genzyme – originally approved by the FDA in 2010.	The FDA approved extensions for the indications of Lumizyme in 2014 (FDA, FDA Approved Drug Products for all products, 2017).
Gazyvaro	Roche/Genentech – originally approved by the EMA in 2014 and by the FDA in 2013.	Extension of indication was approved by the EMA in 2016 and 2017 (refer to Assessment History for this drug on EMA website). Extension of indication was approved by the FDA in 2016 and 2017 (FDA, FDA Approved Drug Products for all products, 2017).

Table 5.24: Details of extensions of indications of some biologic Orphan Drugs.

5.4 APPENDIX 4

Listing of approximate costings of drugs for all biologic and monoclonal antibody Orphan Drugs approved by the FDA and/or the EMA in the period 2010-2017.

Note: all drug costs obtained are publicly quoted and minimal prices.

Note: no pricing information was available for the following Orphan Biologic Drugs – Nexobrid, Zalmoxis (Stem Cell Therapy), Oxervate, Coagadex and Anthim.

Drug (Type)	Cost	Reference	Cost Range
Natpar (biologic)	~$75,000 per year	http://www.bioworld.com/content/shires-faith-nps-pharma-rewarded-natpara-gains-fda-approval	$50-100,000
Adcetris (mAb)	>$80,000	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5330640/	$50-100,000
Elelyso (biologic)	~$150,000	https://www.in-pharmatechnologist.com/Article/2014/07/03/Pfizer-and-Protalix-s-Gaucher-s-drug-gets-kosher-status	$100-150,000
Besponsa (mAb)	>$160,000	https://www.cnbc.com/2017/08/17/reuters-america-brief-pfizer-says-based-on-typical-duration-of-treatment-total-cost-of-besponsa-is-168300.html	$150-200,000
Gazyvaro (mAb)	>$30,000	http://www.ncpe.ie/wp-content/uploads/2016/06/Web-Summary_Obinutuzumab_25-01-2017.pdf	<$50,000
Defitelio (biologic)	>$150,000	https://secure.medicalletter.org/w1503c	$150-200,000

Erwinaze (biologic)	>$150,000	https://www.meds.wiki/erwinaze/	$150-200,000
Sylvant (mAb)	>$7000	https://www.cadth.ca/sites/default/files/pcodr/pcodr_siltuximab_sylvant_mcd_fn_egr.pdf	<$50,000
Darzalex (mAb)	<$100,000	http:/www.myelomabeacon.com/news/2015/11/17/darzalex-daratumumab-fda-approval-multiple-myeloma/	$50-100,000
Vimizim (biologic)	$380,000	https://scrip.pharmaintelligence.informa.com/SC024469/BioMarin-prices-Vimizim-at-1068-per-vial-380k-expected-annual-cost	$200-400,000
Brineura (biologic)	>$700,000	http://www.raredr.com/news/fda-approves-batten-disease-drug	>$400,000
Blincyto (mAb)	>$170,000	https://www.fiercepharma.com/marketing/amgen-slaps-178k-price-on-rare-new-leukemia-drug-blincyto	$150-200,000
Repatha (mAb)	~$14,000	https://www.vox.com/policy-and-politics/2017/3/22/15000840/repatha-cost-side-effects-copay-cholesterol	<$50,000
Kanuma (biologic)	>$300,000	http://www.ibtimes.com/drug-prices-worlds-most-expensive-medicine-costs-440000-year-it-worth-expense-2302609	$200-400,000
Unituxin (mAb)	>$150,000 pa	https://secure.medicalletter.org/w1491f	$100-150,000
Holoclar (biologic)	>$100,000	https://www.nice.org.uk/guidance/ta467/documents/appraisal-consultation-document-2	$100-150,000

Alprolix (biologic)	=~$84,000 x 4 = >$300,000	https://www.medscape.com/viewarticle/879422	$200-400,000
Lartruvo (mAb)	~$17,000 per month. Each cycle is 3 weeks, treatment for up to 8 cycles (24 weeks) – 6 months, cost = <$102,000	https://www.mskcc.org/sites/default/files/node/25097/documents/111516-drug-costs-table.pdf and http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004216/human_med_002036.jsp&mid=WC0b01ac058001d124	$50-100,000
Cyramaza (mAb)	>$7000 a month, >$300,000 per year	https://www.reuters.com/article/us-usa-healthcare-cancer-insight/u-s-cancer-doctors-drop-pricey-drugs-with-little-or-no-effect-idUSKCN0S20DG20151008 and http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002829/human_med_001825.jsp&mid=WC0b01ac058001d124	$200-400,000
Portrazza (mAb)	>$11,000 a month, >$130,000 pa	https://www.wsj.com/articles/lillys-lung-cancer-drug-portrazza-to-cost-11-430-a-month-1449867424 and http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/00388	$100-150,000

		6/human_med_001953.jsp&mid=WC0b01ac058001d124	
Strimvelis (biologic)	>$600,000	http://www.fiercepharma.com/pharma/gsk-inks-money-back-guarantee-665k-strimvelis-blazing-a-trail-for-gene-therapy-pricing	>$400,000
Raxibacumab (mAb)	>$5000 per dose	http://www.latimes.com/nation/la-na-anthrax-resistant-20130519-dto-htmlstory.html	<$50,000
Xiaflex (biologic)	~$30,000	http://www.newyorkurologyspecialists.com/peyronies/xiaflex/insurance/cost-worldwide/	<$50,000
Lumizyme (biologic)	>$48,000 per month, >$500,000 pa	www.fchp.org/providers/pharmacy/~/media/.../Lumizyme_alglucosidasealfa.pdf.ashx	>$400,000
Krystexxa (biologic)	~$5,000 a month, ~$60,000 pa	https://www.reuters.com/article/us-gout-drug/gout-drug-may-help-some-with-few-treatment-options-idUSTRE77I4RI20110819	$50-100,000
Yervoy (mAb)	~$120,000	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3462607/	$100-150,000
Nulojix (biologic)	>$20,000	http://www.nejm.org/doi/full/10.1056/NEJMe1515765?rss=searchAndBrowse#t=article	<$50,000
Opdivo (mAb)	>$110,000	http://www.ncpe.ie/wp-content/uploads/2016/05/Nivolumab-RCC-Summary-final.pdf	$100-150,000

Empliciti (mAb)	>$140,000	https://www.fiercepharma.com/pharma/bristol-myers-puts-a-blockbuster-142k-price-on-new-cancer-med-empliciti	$100-150,000
Adcetris (mAb)	An incremental cost of $85,000	http://www.ncpe.ie/wp-content/uploads/2012/12/Brentuximab-Adcetris-summary.pdf	$50-100,000
Voraxaze (biologic)	3000units cost >$80,000	http://www.pharmacytimes.com/publications/health-system-edition/2013/march2013/glucarpidase-voraxaze	$50-100,000
Myalept (biologic)	>$500,000	http://www.raredr.com/news/myalept-price-500k-600k	>$400,000
Keytruda (mAb)	~$150,000	https://www.nbcnews.com/health/cancer/cancer-drug-keytruda-keeps-some-patients-alive-3-years-n576376	$100-150,000
Praxbind (mAb)	>$3000	https://www.ncbi.nlm.nih.gov/pubmed/27465000	<$50,000
Mepsevii (biologic)	~$375,000	https://www.hayesinc.com/hayes/resource-center/news-service/HNS-20171016-691/	$200-400,000
Hemlibra (mAb)	>$480,000	https://www.fiercepharma.com/regulatory/roche-nabs-pair-blockbuster-fda-approvals-for-hemlibra-gazyva	>$400,000

Table 5.25: Details of costs of Orphan Biologic Drugs

The table below shows the cost range results for **Chemical Orphan Drugs** approved in 2014 to 2017 by either the FDA or the EMA.

Chemical Drug	Approval Date	Cost of Drug per year, min	Cost Range	Reference
Chenodeoxycholic acid	Apr-17	£23.76 per daily dose, $8600 pa	<$50,000	download.eurordis.org/ecrd2012/T7S0706_E_PICAVET.pdf
Cystadrops	Jan-17	<$2000	<$50,000	http://www.cfasi.it/store/1236_Prometheus_Capital.pdf Page 7, converted from Euro to dollars
Rydapt	Sep-17	<$14,000	<$50,000	https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-approvals/drugapprovals_rydapt_2017-0501.pdf
Xermelo	Sep-17	$61,000	$50-100,000	https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-approvals/drugapproval_xermelo_2017-0301.pdf
Galafold	May-16	~$280,000	$200-400,000	http://www.pharmatimes.com/news/nice_backs_amicus_galafold_for_fabry_disease_1183225 converted from sterling to dollars

Ocaliva	Dec-16	<$70,000	$50-100,000	http://www.raredr.com/news/cost-pbc-drug
Onivyde	Oct-16	~$43,000	<$50,000	https://www.bostonglobe.com/business/2015/10/22/fda-approved-merrimack-pharmaceuticals-drug-treat-advanced-pancreatic-cancer/vcV9kMYpQ5gpLr0mVClSZP/story.html
Venclyxto	Dec-16	~$76,000	$50-100,000	https://www.nice.org.uk/guidance/ta487/documents/appraisal-consultation-document converted from sterling to dollars
Wakix	Mar-16	~$19,000	<$50,000	https://www.nice.org.uk/advice/es8/chapter/product-overview
Emflaza	Sep-17	~$89,000	$50-100,000	http://www.raredr.com/news/high-cost-corticosteroids-dmd
Austedo	Apr-17	$60,000	$50-100,000	https://www.fiercepharma.com/pharma/hungry-for-specialty-sales-teva-undercuts-generics-new-huntington-s-med-austedo
Alunbrig	Apr-17	$171,000	$150-200,000	https://www.biopharmadive.com/news/fda-gives-thumbs-up-to-takedas-lung-cancer-drug/441653/
Idhifa	Aug-17	$107,000	$100-150,000	http://www.bioworld.com/content/celgene-agios-win-fda-approval-idh2-targeting-idhifa-aml

Benznidazole	Aug-17	$30,000	<$50,000	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4257633/
Evomela	Mar-16	$24,000	<$50,000	https://prescriptionhope.com/evomela-melphalan/ calculated per annum from 12 month cost
Photrexa	Apr-16	$2850	<$50,000	https://www.reviewofophthalmology.com/article/avedro-takes-heat-for-its-riboflavin-price-increase
Vermox	Oct-16	>$800	<$50,000	https://www.ft.com/content/f0080fe4-c3ad-11e6-9bca-2b93a6856354
Exondys 51	Sept-16	$300,000	$200-400,000	http://www.raredr.com/news/duchenne-drug-to-cost-300k
Rubraca	Dec-16	$13,940 per month, >$167,000 pa	$150-200,000	https://www.fiercepharma.com/pharma/astrazeneca-tesaro-and-clovis-need-to-slash-cost-parp-meds-watchdog-says
Adempas	2014	$9270 per month, >$110,000 pa	$100-150,000	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4218670/
Cerdelga	2015	>$310,000	$200-400,000	https://www.fiercepharma.com/marketing/genzyme-puts-310-250-price-tag-on-new-gaucher-fighting-pill

Cresemba	2015	$70 x 8 days, $560	<$50,000	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5216061/
Deltyba	2014	$142,000	$100-150,000	https://www.ncbi.nlm.nih.gov/pubmed/25862597
Farydak	2015	<$7000	<$50,000	http://www.myelomabeacon.com/news/2015/02/26/farydak-panobinostat-questions-answers-fda-approval/
Hetlioz	2015	>$60,000	$50-100,000	https://www.reuters.com/article/us-health-non24-hetlioz/hetlioz-pill-may-ease-sleep-disorder-for-some-blind-people-idUSKCN0QG25M20150811
Imbruvica	2014	$130,000	$100-150,000	https://www.fiercepharma.com/sales-and-marketing/j-j-pharmacyclics-slap-130-000-price-on-imbruvica-for-rare-lymphoma
Kyprolis	2015	$10,000	<$50,000	http://www.ajmc.com/newsroom/how-much-will-amgens-carfilzomib-combination-treatment-for-multiple-myeloma-cost
Lenvima	2015	>$13,000 pm, >$160,000 pa	$150-200,000	https://www.fool.com/investing/general/2015/03/28/5-freakishly-expensive-cancer-drugs.aspx
Lynparza	2014	$12,450pm, <$150,000 pa	$100-150,000	https://www.fiercepharma.com/marketing/tesaro-undercut-parp-rivals-118k-price-tag-zejula-or-did-it

Ofev	2015	>$37,000	<$50,000	http://www.ncpe.ie/wp-content/uploads/2015/02/Final-summary-22.02.2016.pdf

Table 5.26: Details of costings of Chemical Orphan Drugs

MSc (Biopharmaceutical Science) from the Institute of Technology, Sligo

by Denise McDonald, 2018

Listing of costings for **Non-Orphan Biological Drugs** approved by EMA in 2014-2017

Drug Name	Year Approved	Approx Cost per year	Cost Range	Reference
Obizur	2015	$652,000	>$400,000	https://www.postersessiononline.eu/173580348_eu/congresos/ISTH2017/aula/-PB_126_ISTH2017.pdf
Praluent	2015	$14,000	<$50,000	https://www.vox.com/policy-and-politics/2017/3/22/15000840/repatha-cost-side-effects-copay-cholesterol
Respreeza	2015	>$84,000	$50-100,000	http://www.ncpe.ie/wp-content/uploads/2016/02/NCPE-website-summary_Final.pdf
Taltz	2014	$4104 per inj every 4 weeks, >$50,000 pa	$50-100,000	http://www.rxeconsult.com/healthcare-articles/Taltz-ixekizumab-Dosing-Side-Effects-Cost-And-Prescribing-Information-For-Plaque-Psoriasis---1049/2
Zinbryta (daclizumab)	2016	$87,000	$50-100,000	www.fiercepharma.com/pharma/rep-cummings-to-trump-its-time-to-force-lower-prices-on-biogens-new-ms-drug-zynbryta
Cinqair (reslizumab)	2016	$30,000 pa	<$50,000	www.chicagotribune.com/health/new-biologic-drug-tackles-hard-to-control-asthma

Kevzara (sarilumab)	2017	$39,000	<$50,000	www.fiercepharma.com/ready-their-fda-nod-sanofi-regeneron-set-kevzara-up-for-ra-market-turf-battle
Imfinzi (durvalumab)	2017	$13,000pm, $156,000pa	$150-200,000	www.fiercepharma.com/az-nabs-bladder-cancer-ok-its-first-for-checkpoint-med-imfinzi-can-lung-cancer-nods-follow
Ocrevus (ocrelizumab)	2017	$65,000	$50-100,000	www.drugtopics.modernmedicine.com/drug-topics/news/ms-group-praises-new-drug-despite-high-price-tag
Dupixent (dupilumab)	2017	$37,000	<$50,000	www.fiercepharma-com/marketing/sanofit-and-regeneron-s-dupixent-may-be-a-bargain-at-37k
Siliq (brodalumab)	2017	$3500pm, $30,000pa	<$50,000	www.fiercepharma.com/marketing/valeant-slaps-3-500-sticker-third-to-market-psorias-launch-siliq-
Cosentyx (secuknumab)	2015	>19,000 euro pa ($22,850)	<$50,000	www.independent.ie/irish-news/health/some-80000-people-may-miss-out-on-new-psorias-drug-3156
Entyvio (vedolizumab)	2014	~18,189 euro per patient (~$21,800)	<$50,000	www.ncpe.ie/cost-effectiveness-of-vedolizumab (Entyvio)

Flixabi (infliximab)	2016	<$10,000 pa	<$50,000	www.mims.co.uk/drugs/musculoskeletal-disorders/rheumatoid-arthritis-other autoimmune-disorders/flixabi (100mg cost £377, dosage min 3mg/kg, for an average 70kg patient that means approx. 210mg per dose, dose every 8 weeks (6 times a year), means 1260mg per year dosage, = approx. £4750 = $6437).
Nucala (mepolizumab)	2015	$32,500	<$50,000	www.fiercepharma.com/sales-and-marketing/gsk-s-new-32-500-asthma-med-costs-at-least-2x-too-much-u-s-pricing-watchdog

Table 5.27: Details of costings of non-orphan Biologic Drugs

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