Inês Patrícia Ferreira Amaral

ORPHAN DRUGS

REGULATORY FRAMEWORK, MARKET POSITIONING AND MAJOR DEVELOPMENT CHALLENGES AND STRATEGIES

Dissertação de Mestrado em Biotecnologia Farmacêutica, orientada pela Professora Doutora Maria Dulce Cotrim e pela Doutora Ana Catarina Pinto (Bluepharma, Indústria Farmacêutica SA) e apresentada à Faculdade de Farmácia da Universidade de Coimbra

Julho 2016

· U C ·

Universidade de Coimbra

Inês Patrícia Ferreira Amaral

ORPHAN DRUGS

REGULATORY FRAMEWORK, MARKET POSITIONING AND MAJOR DEVELOPMENT CHALLENGES AND STRATEGIES

Dissertação de Mestrado em Biotecnologia Farmacêutica, orientada pela Professora Doutora Maria Dulce Cotrim e pela Doutora Ana Catarina Pinto (Bluepharma, Indústria Farmacêutica SA) e apresentada à Faculdade de Farmácia da Universidade de Coimbra

Julho 2016

· U C ·

UNIVERSIDADE DE COIMBRA

Agradecimentos

Nesta fase várias foram as pessoas que passaram na minha vida e por uma ou por outra razão deixaram um pequeno pedaço de si. No entanto quero agradecer, em particular:

À Professora Doutora Maria Dulce Cotrim, Professora da Faculdade de Farmácia da Universidade de Coimbra, por se ter disponibilizado para orientar esta dissertação.

Ao Professor Doutor Sérgio Simões, Professor da Faculdade de Farmácia da Universidade de Coimbra e Chairman da Luzitin S.A, por me ter dado o prazer de concretizar este trabalho em parceria com a Luzitin.

À Doutora Ana Catarina Pinto, orientadora desta dissertação na Luzitin, por toda a disponibilidade, dedicação, apoio incondicional, compreensão ao longo do trabalho e principalmente por estar sempre presente na orientação desta minha dissertação.

Aos meus pais, que vivem comigo desde sempre as alegrias e tristezas desta caminhada, sem vocês isto não tinha sentido. Agradeço todo o esforço que fazem para tornarem possível a realização dos meus desejos, por todos os valores que me transmitem e toda a preocupação que têm comigo.

À minha irmã, que será sempre a minha eterna companheira. Pela força transmitida e compreensão. Por estar ao meu lado em todos os momentos da minha vida.

À minha avó, que me transmite muita força e que me faz acreditar nos meus sonhos.

À minha "família" Bluepharma & Luzitin, agradeço o apoio e o interesse sempre manifestados. Em especial, agradeço aos meus colegas do departamento de Assuntos Regulamentares pela paciência e pelas palavras de incentivo dia após dia.

Por fim, a todos os meus amigos que sempre demonstraram o valor da amizade e que com interesse acompanharam e indagaram o decorrer dos meus estudos académicos.

A todos eles o meu muito sincero, obrigada!

"Rare disease are rare, but
Rare disease patients are numerous"
(Orphanet)

Abstract

Orphan Drug is a pharmaceutical product aimed at a rare disease. In the world, there are more than 6000 rare diseases; 80% of them are of genetic origin, and are often chronic and life-threatening debilitating conditions with extremely low prevalence for which there is no medication, diagnosis, prevention and/or satisfactory treatment.
The availability of Orphan Drugs in the Market may depend on the legislation and regulations of each country individually and regulations including national Orphan Drug policies, Orphan Drug designation, Marketing Authorisation requirements. Therefore, it is very important to understand the Orphan Drug environment in order to improve research and policy development for the treatment of rare diseases.

Currently, biotechnology can provide powerful tools to develop diagnostics and treatments for orphan diseases. Orphan drugs are highly innovative, especially compared to the new molecular entities that did not receive orphan designation.
The number of orphan drugs approved each year appears to be increasing and orphan drugs obtained from biotechnology are gaining importance and market share, although orphan small molecules still dominate. Repatha® (evolocumab) – a human monoclonal antibody (mAb), which FDA granted the orphan drug designation for homozygous familial hypercholesterolemia in 2013, received marketing authorisation in 2015 for this orphan disease. As it exhibits an innovative mechanism of action and since its market forecast for 2020 is very significant, this new drug is presented in this thesis as a successful case study.

In order to benefit from the regulatory and commercial incentives of orphan drug development, sponsors must be aware of the hurdles involved in developing drugs for rare diseases. Clinical trials involving therapies for rare diseases are challenging for various reasons, such as the very low or exceptionally reduced prevalence of these diseases, small and heterogeneous patient populations, difficulty in recruiting and high attrition rates during R&D processes. The present thesis discusses the main difficulties and challenges in developing an orphan drug, with particular focus on clinical development.

In summary, the main objectives of this dissertation are:

- To provide a review of the regulatory framework from different Authorities around the world concerning Orphan Drug Designation;
- To evaluate biotechnology contribution in the development of drugs for rare diseases;
- To present the recently approved drug Repatha® (evolocumab) as a case study;
- To describe the specificities of Orphan Drug development, namely clinical development challenges and strategies.

Keywords:
Orphan Drug, Rare Disease, EMA, FDA, Japan, Biotechnology, Clinical studies.

Resumo

Um Medicamento Órfão é um produto farmacêutico que se destina a uma doença rara. No mundo existem mais de 6000 doenças raras; 80% das quais de origem genética, e que são condições debilitantes crónicas e/ou mortais. Tratam-se de doenças que apresentam uma prevalência extremamente baixa e para as quais não existe medicação, diagnóstico, prevenção e/ou tratamento satisfatório.

A disponibilidade de Medicamentos Órfãos no mercado pode depender da legislação e regulamentação de cada país, incluindo a sua política nacional e o processo de designação de Medicamentos Órfãos e os requisitos de autorização de mercado. Assim, é muito importante compreender o enquadramento regulamentar dos Medicamentos Órfãos a fim de melhorar a investigação e a política de desenvolvimento destes produtos para Doenças Raras.

Atualmente, a biotecnologia pode fornecer ferramentas importantes para o desenvolvimento de meios de diagnóstico e tratamentos para Doenças Raras. Medicamentos Órfãos são medicamentos altamente inovadores, especialmente quando comparados com as novas entidades moleculares que não receberam o estatuto de medicamento órfão.

O número de Medicamentos Órfãos aprovados a cada ano tem vindo a aumentar e constata-se que os medicamentos órfãos obtidos através da biotecnologia estão a ganhar importância e quota de mercado, apesar de os medicamentos órfãos de origem química ainda dominarem o mesmo. Repatha® (evolocumab) – um anticorpo monoclonal humano (MAB), ao qual a FDA concedeu a designação de Medicamento Órfão em 2013 para o tratamento de Hipercolesterolemia Familiar Homozigótica, obteve a autorização de comercialização em 2015 para esta doença órfã. Dado que este fármaco apresenta um mecanismo de ação inovador e, uma vez que a sua previsão para 2020 é de um mercado muito significativo, este novo fármaco é apresentado nesta tese como um caso de estudo de sucesso.

A fim de beneficiar dos incentivos regulamentares e comerciais atribuídos ao desenvolvimento de medicamentos órfãos, os promotores devem estar cientes dos obstáculos envolvidos no desenvolvimento destes medicamentos. Ensaios clínicos envolvendo terapias para doenças raras são um desafio por várias razões, tais como a

prevalência muito baixa, ou, excecionalmente reduzida destas doenças, populações pequenas e heterogéneas de doentes, dificuldade no recrutamento e taxas de atrito elevadas durante os processos de R&D. A presente tese apresenta e discute as principais dificuldades e desafios no desenvolvimento de um medicamento órfão, com especial enfoque no desenvolvimento clínico.

Em resumo, os principais objetivos desta tese são:

- Realizar uma revisão do enquadramento regulamentar das diferentes autoridades a nível mundial relativamente à atribuição da designação de medicamento órfão;
- Avaliar a contribuição da biotecnologia no desenvolvimento de medicamentos para as doenças raras;
- Apresentar, como caso de estudo, o fármaco recentemente aprovado Repatha® (evolocumab);
- Descrever as especificidades do desenvolvimento de medicamentos órfãos, nomeadamente os desafios e estratégias durante o desenvolvimento clínico.

Palavras-chave:
Medicamentos Órfãos, Doenças Raras, EMA, FDA, Japão, Biotecnologia, Estudos clínicos.

Abbreviations

AA	Accelerated Approval
CAGR	Compound Annual Growth Rate
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human
COMP	Committee for Orphan Medicinal Products
EC	European Commission
EMA	European Medicines Agency
EU	Europe Union
EURORDIS	European Rare Disease Organization
FDA	Food Drug Designation
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
LDL	Low Density Lipoprotein
LDLR	Low Density Lipoprotein Receptor
mAb	Monoclonal antibody
MHLW	Ministry of Health, Labour and Welfare
NIBIP	National Institute of Biomedical Innovation
NORD	National Organization for Rare Disorders
OD	Orphan Drug
ODA	Orphan Drug Act
ODD	Orphan Drug Designation
OMP	Orphan Medicinal Products
OOPD	Office of Orphan Product Development
PDUFA	Prescription Drug User Fee Act
PMDA	Pharmaceuticals and Medical Devices Agency
POC	Proof-of-Concept
R&D	Research and Development
RDs	Rare Diseases
SAWP	Scientific Advice Working Party
SME	Small-medium enterprise
USA	United States of America

Table of contents

List of Figures

List of Tables

Thesis Organization

The following thesis is structured in five different chapters:

In **Chapter 1**, a general introduction to the following chapters (Chapters 2-4) is presented, according to recent literature overview concerning the Rare Diseases and Orphan Drugs. This chapter is important to understand, briefly, the main differences among the main legislative systems in the United States of America (USA), European Union (EU) and Japan, although they are working to improve the international collaboration in the field of orphan drug development for unmet medical needs.

Chapter 2 describes and compares in detail the Orphan Drug regulations and opportunities that currently exist in the USA, EU and Japan. The incentives included in the orphan drug legislations or policies, the criteria for designation of orphan status and the authorisation process of an orphan drug are also described and compared.

Chapter 3 is focused on the pharmaceutical market. This chapter aims to study the positioning of orphan drugs, especially biotechnology-derived orphan drugs. The top selling Orphan Drugs in the World are reported and the expected market for 2020 is discussed. Repatha® (evolocumab) – a human monoclonal antibody (mAb), approved in 2015, is presented as a successful case study of a medicinal product resultant from biotechnology which was granted with orphan designation and reached the market with promising market forecast.

There are several challenges associated with Orphan Drug development, especially during clinical study preparation and conduction. These challenges and some strategies to overcome them are reported in **Chapter 4.**

Finally, **Chapter 5** summarizes the most relevant conclusions obtained in the preceding chapters. In this chapter it is also presented a reflection on future perspectives concerning Orphan Drugs.

Chapter 1 - General Introduction

Today, more than ever, researchers are focused on providing care for the rare diseases that may have been overlooked in the past due to the challenges of conducting clinical trials in small populations and to the limited commercialization potential [1]. Rare Diseases (RDs) affect millions of people and medications for the approximately 7,000 rare diseases in the world account for less than 10% of global pharmaceutical spending [2]. The growing number of rare diseases awaiting treatment are an important public health issue.

1.1 Rare Diseases

Rare diseases are characterized by a wide diversity of symptoms and signs that vary not only from disease to disease but also from patient to patient suffering from the same disease [3]. Most of these conditions are serious and life-altering and many others are life-threatening or fatal [4].

An "orphan" disease is a disease that is "forgotten" by treatment, a disease for which there is no definitive, convincing treatment. Orphan is used mainly in the context of an indication, with emphasis on "intervention" or its absence. There may be measures available to attenuate the symptoms or risks for complications, but there is nothing to change or prolong the natural course of the disease or to eliminate the damage caused by it. A disease can be rare, but not orphan, if there is an effective treatment available. A rare disease, if harmless and with good self-healing prognosis, may not be an objective for industrial drug/ treatment development. In a rare disease, the costs for development of a new therapy are seen in relation to a very small number of individual patients. The price per prescription may become astronomical. A frequent disease can be orphan, if there is no treatment. An "orphan drug" then is one for a rare disease for which there are no adequate drug is available, according to the US Orphan Drug Act definition [5].

Some rare conditions are extremely rare, with the number of reported cases in the single or low double digits. Others occur in hundreds, thousands, or tens of thousands of people [4]. The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis and difficult access to care. This results in additional physical, psychological and intellectual impairments, inadequate or even harmful treatments and loss of confidence in the health care system, despite the fact that some rare diseases are compatible with a normal life if diagnosed on time and properly managed. Misdiagnosis and

non-diagnosis are the main hurdles to improving life-quality for thousands of rare disease patients [6].

The definition of a rare disease varies and there is no universally accepted definition. In the European Union (EU), rare diseases are defined as life-threatening or chronic debilitating conditions that affect less than 5 in 10,000 persons; in the United States of America (USA), rare diseases are defined as those diseases that affect less than 200,000 persons; and the definition shifts to an affected population of less than 50,000 in Japan. Compared to the EU, USA and Japan, the World Health Organization (WHO) defines a rare disease based on a higher prevalence: less than 6.5–10 in 10,000 [7].

Given the low incidence and prevalence of these diseases, they individually reach only a small percentage of the global population; together, however, they affect between 6% and 8% (or 420 million to 560 million people), thus imposing a significant global burden. Approximately 80% of rare diseases have a genetic origin. The remainder is the result of bacterial and viral infections, allergies or degenerative conditions [2]. Some rare diseases are also caused by a combination of genetic and environmental factors [8]. Most rare diseases (75%) are manifested early in life and affect children from 0 to 5 years of age. They also contribute significantly to morbidity and mortality in the first 18 years of life [2].

The thousands of different pathologies defined as "rare" have in common specific features that enhance patient vulnerability [9]:

- Low prevalence thus the isolation and marginalisation of patients affected by them;
- Heterogeneity of diseases with different research needs and therapeutic responses;
- The complexity of diseases often affecting different organs thus requiring multidisciplinary responses;
- Research is actually conducted only on a small number of inventoried diseases;
- Fragmented knowledge or no knowledge at all on the pathogenesis/pathophysiological mechanisms and epidemiology of many RDs, which make diagnosis difficult to make and therapy slow to develop;
- Frequently incorrect diagnosis, reduced life expectancy and critical transition from pediatric to adult healthcare are additional features making RD patient especially vulnerable individuals.

Research in orphan diseases was until recently carried out mainly by academic institutions, biotech companies and smaller, specialty devoted drug companies. Large pharmaceutical corporations have also lately taken interest, mainly for exploiting the orphan drug legislations by targeting sub-groups of common diseases [10].

In-depth understanding of the disease helps sponsors (pharmaceutical companies or others) avoid mistakes that may be costly in time and resources. Efficient study of the small number of affected patients may be guided better by greater understanding of the disease. A natural history study can provide critical information to guide every stage of drug development from drug discovery to determining effectiveness and safety of the drug in treating a disease [11].

Knowledge about the disease's natural history can inform and impact important aspects of drug development including [11]:

- Defining the disease population, including a description of the full range of disease manifestations and identification of important disease subtypes. Understanding and implementation of critical elements in clinical study design, such as study duration and choice of subpopulations;
- Developing and selecting outcome measures that are more specific or sensitive to changes in the manifestations of the disease or more quickly demonstrate safety or efficacy than existing measures;
- Developing new or optimized biomarkers that may provide proof-of-concept (POC) information, guide dose selection, allow early recognition of safety concerns, or provide supportive evidence of efficacy;
- In some cases, biomarkers can be used as for surrogate endpoints, allowing the evaluation of outcomes earlier during clinical developed [12].

Recent advances in medical science have enhanced the understanding of these disorders at the biochemical and pathophysiologic levels and created more opportunities to address unmet needs by developing specific therapeutic options for RD patients. Adapting the development process for these RDs is now an important part of the rarest and most difficult-to-treat rare diseases have specific drugs developed [12].

1.2 Orphan Drugs and global efforts to improve their development

Orphan Medicinal Products (OMP) also commonly called orphan drugs (OD) are medicinal products intended for diagnosis, prevention or treatment of life-threatening or debilitating rare diseases with extremely low prevalence for which there is no medication, diagnosis, prevention and/or satisfactory treatment. These drugs are called orphans because most pharmaceutical industries have little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition for which the expected returns would be too low [13].

There are difficulties in balancing the urgent need for drugs to treat rare diseases with the requirements for guaranteed quality, efficacy and safety and, when necessary, making comparisons with existing approved therapies [14].

To provide care for people with a rare disease and to encourage pharmaceutical and biotechnology companies to invest in treatment for rare diseases, governments have created various legal and financial incentives [15]. When the Orphan Drug Act (ODA) was signed into law on January 4th 1983, the USA became the first country in the world to provide incentives for developing treatments for rare diseases. Since then Japan and the European Union (EU) have instituted provisions similar to the ODA to support the development of orphan drugs (Figure 1) [16].

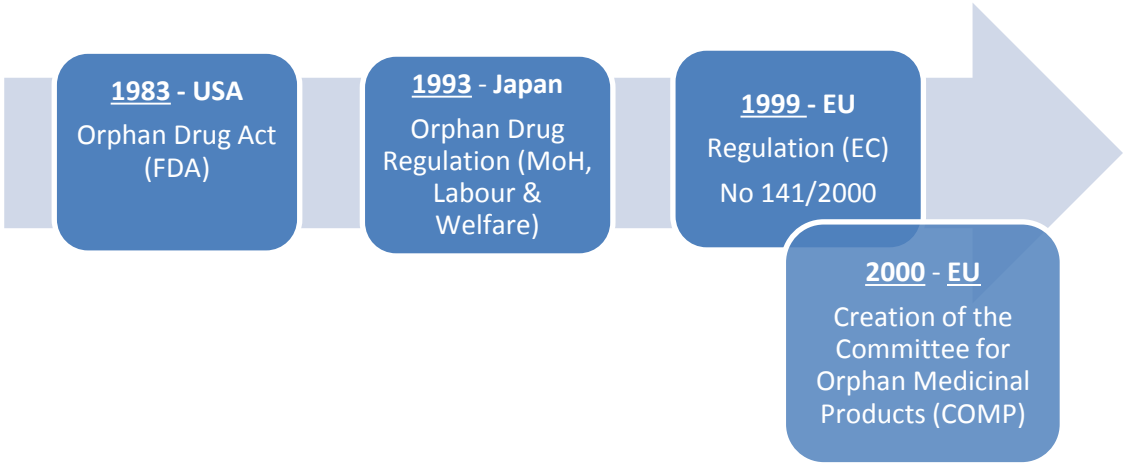


Figure 1. History of Orphan medicines legislations in the USA, Japan and EU
Data was adapted from [2, 3].

The EMA has been engaged in collaborations with the FDA's Office of Orphan Products Development (OOPD) since 2000 and with the Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) Orphan Drug

Designation Service since 2010. Identifying areas of similarity among these programmes has led to activities aimed at reducing redundancies and the administrative load for sponsors interested in submitting applications for orphan drug designation in each region, allowing for transparency and an increased sponsor understanding of each agency's processes and incentives [17].

The Orphan Drug legislation recognises "the expected potential" of an OMP in the treatment of a rare disease by granting a status referred to as orphan designation. A sponsor obtains orphan designation for their medicinal product by submitting an application to a designating authority, prior to applying for a marketing authorisation application [18].

Prior to enactment of the ODA, very few orphan drugs were available on the market to treat patients with rare diseases. A combination of market and regulatory barriers limited the ability of drug developers to bring new orphan drugs to market, and, while many of those barriers remain in place today, the efforts of governments, international organizations as well as many other national governmental and non-governmental organizations are continuously improving health standards worldwide and global health care is becoming a reality [14]. As shown in Figure 2, in the last decades, the number of orphan drugs designations has increased dramatically, especially since 2003. The ODD process in Japan and Europe only started in 1993 and 2000, respectively. The last data regarding 2014 shows that USA orphan designations increase 12%; European designations up 62% and Japan designations up 7%.

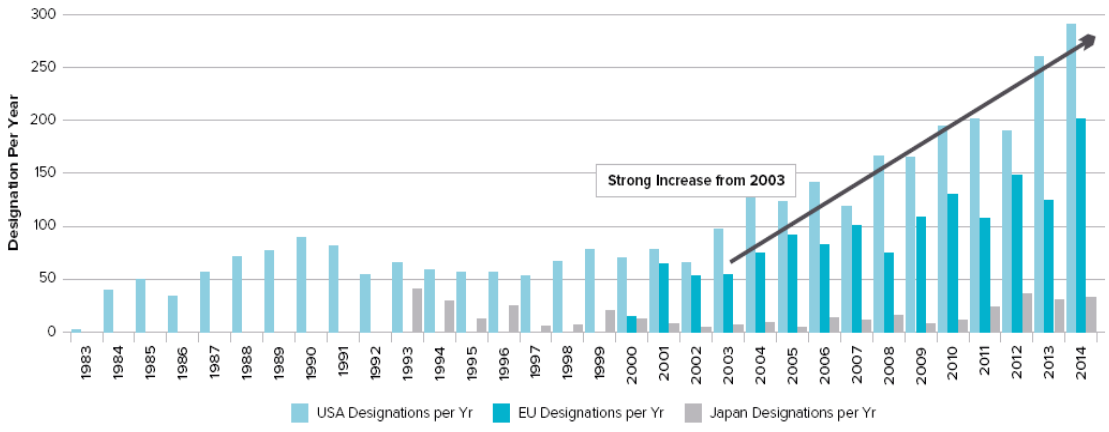


Figure 2. USA, EU & Japan Designation per Year (1983-2014)
Reproduced from [19].

As shown in Figure 3, the trends and identified differences in granted orphan drug designations and holding orphan drug designations among the USA, EU, and Japan following the implementation of legislation are characterized by region. Given that the EU had adopted the legislation most recently (in 2000), it has been rapidly and intensively focusing its attention on orphan drug designations.

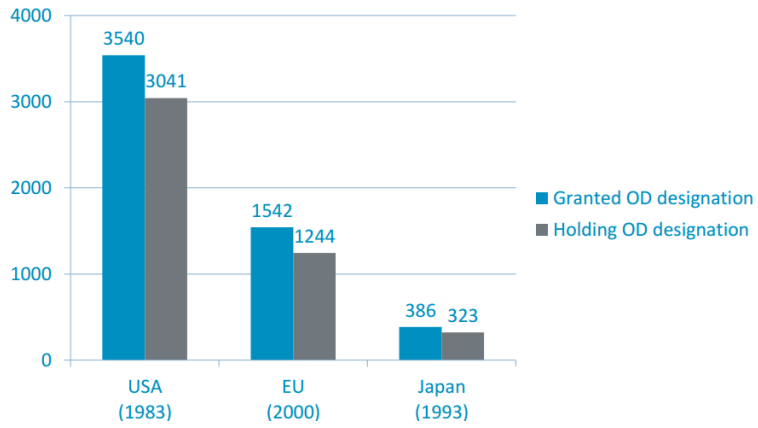


Figure 3. Trends and identified differences in granted orphan drug designations and holding orphan drug designations among the USA, EU, and Japan
Reproduced from [20].

Orphan legislations have been developed in various constituencies and have a worldwide synergistic effect on development. At global level, orphan medicines are developed following similar regulatory and scientific requirements. Taking stock of the situation, regulators have started collaborating to develop systems for exchange of information on procedures and regulatory practices. The final goal is to facilitate the development and marketing in different jurisdictions by setting a more fluid communication, closer collaboration, administrative simplification and mutual understanding to achieve finally as much voluntary harmonisation as possible [21].

The primary challenge is to balance patient demand with the rising costs in the drug development industry due to scientific and technological advancements [2]. The rights of people with rare diseases and their families are a complex and comprehensive issue with various legal forms, depending on the patient's condition (taxation, support, allowances, pensions, transport, employment, labor law, etc.) [21]. Patient Associations and various organisations are creating awareness on rare diseases and are also pushing governments in bringing legislation acts for better quality of life [22].

Patients' representatives have an increasingly present voice in all aspects of drug development from fundamental research through regulatory processes to health technology assessment. Although major advances have been made in raising awareness and increasing funding for rare diseases, important challenges remain in terms of best use of resources, coordinating efforts and improving policy. The importance of including patients' groups in fundamental and clinical research as equal partners has become a fact that clearly contributes to the success of an application and the research conducted [23].

Three of the biggest organisations in the world focused on rare diseases are [24]:

- European Rare Disease Organization (EURORDIS) which is the voice of rare disease patients in Europe;
- National Organization for Rare Diseases (NORD) – An American National Organization for Rare Disorders;
- Orphanet that is an organization which works in over 40 countries, collecting information on rare diseases from expert centers, medical laboratories, ongoing research projects and patient organisations.

Other national federations, such as FEDRA – Portuguese Federation of Rare Diseases ("Federação Portuguesa de Doenças Raras"), encourage disease-specific patient advocacy organizations in other countries to establish a national umbrella organization to unite rare disease patient advocates [24].

Rare Disease Day, celebrated annually on February 28th or 29th, established in Europe by EURORDIS in 2008, is one of the most successful initiatives to promote global collaboration among rare disease patient advocacy organizations [16]. The following year, NORD became a partner to extend the initiative into the USA, and groups from several other regions participated as well. Today, dozens of countries host Rare Disease Day events, with more countries getting involved each year [25].

Global collaboration is also taking place among other stakeholder groups not specifically limited to patient organizations. The International Conference on Rare Diseases and Orphan Products was established in 2005 to host global conferences drawing together government research institutes, academic partners, and patient organizations [16].

In conclusion, the development of treatment strategies for rare diseases and the development of orphan drugs may be considered to be one of the major challenge for global

health systems. The term "orphan drugs" was introduced by governments of developed countries to help in the production and marketing of medicinal drugs by the pharmaceutical industry for patients suffering from rare conditions living in their own countries [10]. Over the last years, there has been a raising interest by the health care system stakeholders in the diagnosis and treatment of disorders with a low prevalence [26]. Fortunately, the tides are beginning to turn towards a more favorable view of collaboration among leading researchers and institutions, spurred on in part by governmental initiatives that recognize how essential multiple resources are to solve large and complex problems [27]. Research on rare diseases is also important since these diseases can serve as models for more common diseases and the complexity of rare diseases often requires multidisciplinary innovative approaches [28].

Chapter 2 - Regulatory Framework for the development of orphan drugs

2.1 Legal Framework and orphan drug designation application in the European Union

Rare diseases in the European Union (EU) are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people. About 30 million people living in the EU suffer from a rare disease. This is equivalent to around 250,000 people or less for each disease [29]. The development of orphan medicinal products is therefore an important consideration for public health policymakers seeking to address patients' needs [30].

Rare Diseases were identified, for the first time, as a priority field for public health action in the EU, in the Commission Communication of 24 November 1993 on the framework for action in the field of public health. This was followed by providing support for several projects as well as by setting up the Rare Diseases Task Force [31].

On 23 February 1995, at the instigation of the European Commission (EC) department Responsible for science, R&D and industry, an expert group was formed with the objective of discussing recommendations on priorities for EU level research and regulatory action in the field of rare diseases and orphan drugs. The United States' effective Orphan Drug Act was taken as an example of what could be done. Commission proposals and strong political backing from the Council and the European Parliament led to the adoption of the Orphan Regulation (EC) No 141/200 on 16 December 1999 which was published in the Official Journal of the European Communities on 22 January 2000 [30].

The European Medicines Agency (EMA) has specific committees that carry out its scientific assessments. As shown in Figure 4, concerning the OMP, COMP and CHMP have an important role in the legal framework on Orphan Drug Designation application evaluation and Marketing Authorisation of orphan drug, respectively, in the EU. The EU is unique in that it is the only entity to have a centralised procedure for orphan drug designation and marketing approval extending across its member countries [32].

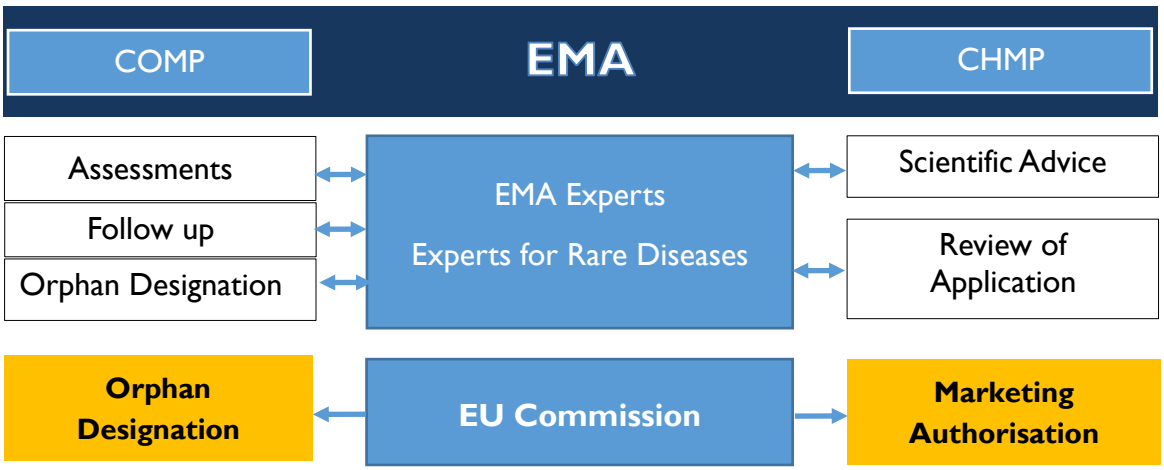


Figure 4. The EMA committees which are responsible on the Orphan Drug Designation evaluation and Marketing Authorisation procedures in Europe
Adapted from [33].

2.1.1 Orphan Medical Product Designation in the EU

The first step in the development of any Orphan Medicinal Product is to obtain the respective designation. According to the EMA, to qualify for orphan designation, a medicine must meet all of the following criteria [34]:

1. "it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
2. the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
3. no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition".

In order to request the designation as an Orphan Medicinal Product, a sponsor shall submit to the EMA a complete application. The format and content of applications were stablished by Authority and the forms are available in EMA's website [35]. Since 2000, the European Commission adopted several guideline documents and communications clarifying issues related to the agency's interpretation of the regulations, assessing similarity of medicinal products and reviewing market exclusivity [35].

Since 2015, sponsor applicant are no longer required to send a notification of intent to file an orphan drug application for designation to the EMA. A sponsor should follow or submit

the application to the EMA or request a pre-submission meeting/teleconference. The Agency strongly encourages sponsors to request a pre-submission meeting via teleconference with the Agency prior to filing an application [35].

After submission, the coordinators prepare a summary report on the application, which is circulated to all Committee for Orphan Medicinal Products (COMP) members [36]. The opinions on orphan designation are adopted by the COMP at their monthly meetings at the EMA (Post-orphan medicinal product designation procedures, 2016). The COMP will either adopt a positive opinion or raise a list of questions and invite the sponsor to an oral explanation at the next COMP plenary meeting [35].

When the outcome for a designation application is negative, the COMP will adopt a negative opinion, unless the sponsor chooses to withdraw the application. The sponsor must inform the Agency in writing of the withdrawal before the end of the COMP meeting and then, no information on the application is made public. The sponsor can re-apply for orphan designation with additional or complementary data at a later stage. If the sponsor does not withdraw, a negative opinion is adopted by the COMP [36].

The evaluation process has a maximum duration of 90 days and in examining an application, the COMP will focus on determining whether the sponsor has established that all the several designation criteria are met [36]:

• The life-threatening or debilitating nature of the condition

Recognised distinct medical entities are generally considered valid conditions. Different degrees of severity or stages of a disease are generally not considered as distinct condition and the fact that a subset of patients exists in whom the medicinal product is expected to show a favourable benefit/risk would generally not be sufficient to define a distinct condition (unless patients in that subset present with distinct and unique characteristics that are essential for the medicinal product to carry out its action) [18].

• That the prevalence of the condition in the European Union is not more than 5 in 10,000

Prevalence is defined as the number of persons with a disease or condition at a specific instant in time in a given population. However, in many cases the true prevalence is not

known and will be based on an estimated prevalence. EMA provides points to consider on a document entitled "Calculation and Reporting of the Prevalence of a Condition for Orphan Designation (COMP/436/01)" [18].

• The medical plausibility of the proposed orphan indication

Medical plausibility is not an explicit designation criteria but the Regulation implies a scientific need to consider medical plausibility. There must be a strong scientific rationale for the use of the product in the proposed orphan indication. EMA expects that the sponsor submits studies (preclinical or clinical) that evidence the medical plausibility of the proposed drug on the orphan condition. EMA provides a guidance entitled "Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation" (EMA/COMP/15893/2009) [18].

• That no satisfactory method of diagnosis prevention or treatment exists, or if such a method exists, that the medicinal product will be of significant benefit to those affected by the condition

The concept of significant benefit is not considered if there are no available treatment options for the condition. Significant benefit is defined as a clinically relevant advantage or major contribution to patient care. It should be based on assumptions at the time of orphan designation and on sound scientific principles [18]. The EMA requests that sponsors explain the current status of the product development programme as well as regulatory considerations associated with orphan drug designation [17].

Following adoption of an opinion (negative or positive) on orphan medicinal product designation by the COMP, this opinion is forwarded to the European Commission (EC) and the sponsor. The decision on the designation is adopted or not by the EC within 30 days of receipt of the COMP opinion and the decision is forwarded to the sponsor. Upon a favorable decision by the EC, the designated OMP medicinal product enters the Community Register and a public summary of opinion on orphan designation is published on the EMA website, which contains a searchable list of all opinions on applications for OMP designation. EC decisions on refusal of designation are published in the Community Register under orphan medicinal products refused link [35, 37].

As shown in Table 1, between 2000 and 2015, the EMA received 2385 applications for ODD. EMA gave 1607 positive opinions and the great majority of the applications forward to the EC received OMP designation (1596).

Table 1. Status of ODD Applications in the EU
Adapted from [38].

	2000-2005	2006-2010	2011	2012	2013	2014	2015	Total
Application submitted	548	689	166	197	201	329	258	**2385**
Positive COMP Opinions	348	500	111	139	136	196	177	**1607**
Negative COMP Opinions	8	6	2	1	1	2	1	**21**
EC Designation	343	485	107	148	136	187	190	**1596**
Withdrawals During assessment	150	144	45	52	60	62	94	**607**

OD designations data compiled from EMA's database showed that, since 2000 until May 2015, the number of OD designations per year is continuously growing and only 1% of submissions has been rejected by the COMP (Figure 5).

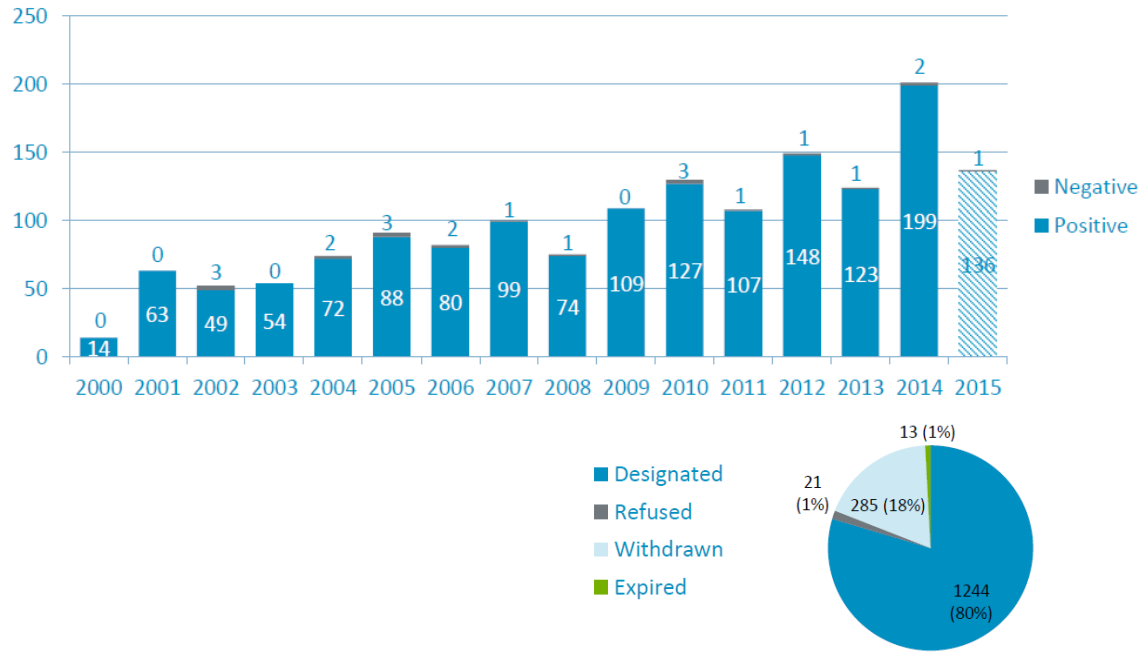


Figure 5. OD designation granted in the EU (2000-2015)
Reproduced from [20].

2.1.2 Post-Orphan Medicinal Product Designation – incentives and supporting programmes

The EU Regulation on orphan medicinal products establishes a centralised procedure for the designation and puts in place incentives for their research, marketing and development products [39].

The principal incentives introduced by the Orphan Regulation are the following:

a) Protocol Assistance

The EMA provides protocol assistance (designation of the scientific advice given to orphan products) about the various tests and clinical trials necessary for drug development to pharmaceutical companies. This information is delivered at no cost (in case the sponsor is a small-medium enterprise) or at reduced fee to optimize the development of orphan drugs and to ensure better compliance with the European regulatory requirements [39].

The Scientific Advice Working Party (SAWP) is a standing working party with the sole remit of providing scientific advice and protocol assistance. It was established by the Committee for Medicinal Products for Human Use Human Use (CHMP) [40]. In 2015, 163 pre-submission meetings were conducted with applicants to advise them on their request for orphan designation [41].

b) Fee Reduction

During the approval process fee waivers for orphan medicinal products and reduced fees are granted. These apply to marketing authorisation, inspections, variations and protocol assistance [39].

c) Market exclusivity

When an orphan product receives a marketing authorisation in the EU, competitive similar products cannot be placed on the market for 10 years after receiving marketing authorisation. In the case of pediatric drugs the protection is extended to 12 years [39].

d) Additional incentives

Companies classified as small or medium-sized enterprise (SMEs) benefit from further incentives when developing medicines with orphan designation. These include administrative and procedural assistance from the Agency's SME office and fee reductions [32].

e) Grants

The Agency does not offer research grants for sponsors of orphan medicines, but funding is available from the EC and other sources via e.g.:

• Horizon 2020, the EU Framework Programme for Research and Innovation Sponsors;

• E-Rare, a European transnational project for research programmes on rare diseases [37].

f) Incentives in Member States

Most Member States reported other measures that they have taken under national plans on rare diseases that cover not only OMPs, but also the prevention (e.g. pre-natal diagnosis) and detection of rare diseases, the exchange of information and cooperation with patients' organisations. For example, Germany has put in place a number of measures, such as fee reductions for activities involving medicinal products targeting rare diseases or under its national research programme [30].

In parallel to the implementation of the Orphan Regulation, the awareness of rare diseases has increased remarkably across the EU, as well as the public support via the establishment of structures of networking and research. Good examples of this advance are the disease-dedicated networks created under the auspices of the EU framework programme and the health programme (e.g. Together Against Genodermatoses, European Network of Paediatric Hodgkin's Lymphoma, European Network of Reference for Rare Paediatric Neurological Diseases, Reference Network for Langerhans Cell Histiocytosis and Associated Syndromes).
The EC, which manages the programmes, is ensuring continuous support in the health programme for the period 2013 – 2020. Rare diseases are kept as one of the priority areas of the public health agenda. At the institutional level, this is mirrored by the establishment of new structures such as the EU Committee of Experts on Rare Diseases (EUCERD) and the International Rare Diseases Research Consortium (IRDIRC), while maintaining and developing Orphanet [21].

2.1.3 Post-Orphan Medicinal Product Designation – the road until Marketing Authorisation

Under Regulation (EC) No 141/2000, sponsors must submit an annual report on development to the Agency summarising the status of development of the OMP and the future development plan for the next year. This annual report has to be submitted by the sponsor every year until Marketing Authorisation (MA) is granted [42].

Once a sponsor with a medicine with orphan designation has generated the data which can be considered adequate MA Application can be submitted [43].
Applications for MA for designated orphan medicines are assessed by the CHMP and the maximum timeframe under the Centralised Procedure is 210 days [37]. It is very important to highlight the fact that an orphan designation by the COMP does not constitute a marketing authorisation [44]. Sponsors need to submit an application for maintenance of the orphan designation in order to be eligible for the ten-year market exclusivity incentive and may also need to submit an evaluation of orphan similarity [45]. This report includes data on [46]:

- the current prevalence of the condition to be diagnosed, prevented or treated, or the potential return on investment;
- the current life-threatening or debilitating nature of the condition;
- the current existence of other methods for the diagnosis, prevention or treatment of the condition;
- if applicable, a justification of the medicine's significant benefit.

While decisions on OMP designation and marketing authorisation are made at the European Union level, reimbursement decisions are made at the national level. OMP value and affordability are high priority issues for policymakers and decisions regarding their pricing and funding are highly complex. There is currently no European consensus on how OMP value should be assessed and inequalities of access to OMPs have previously been observed. Against this background, policy makers in many countries are considering reforms to improve access to OMPs [47].

The European Orphan Medicinal Products Regulation has successfully encouraged research to develop treatments for rare diseases resulting in the authorisation of new OMPs in Europe [35]. Since 2001 from May 2015, 126 (8%) designated ODs have been initially approved, 4 OD have been subsequently withdrawn and only 10 (7%) molecules were refused in granting a MA (Figure 6).

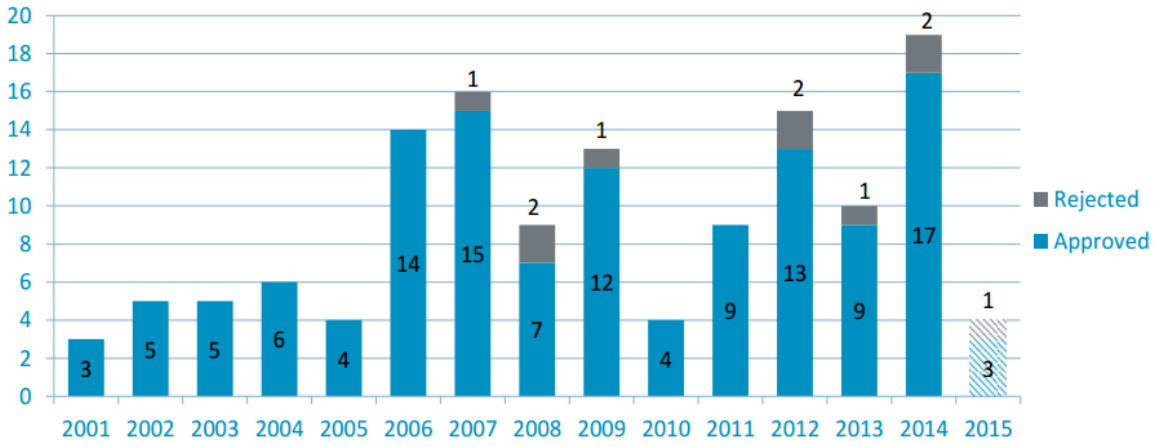


Figure 6. OMP that received or have been rejected for Marketing Authorisation in EU
Reproduced from [20].

Additionally, and to provide updated information Table 2 presents, individually, the Orphan Medicinal Products that received Marketing Authorisation in Europe since 2015 until April 2016.

Table 2. Orphan Medicinal Products granted with Marketing Authorisation in EU since 2015 until April 2016

Adapted from [48, 49].

Drug Name	Active Ingredient	Orphan Designation Date	Marketing Authorisation Date	Approved indication
Ofev	nintedanib	26/04/2013	19/01/2015	Treatment of Idiopathic Pulmonary Fibrosis (IPF)
Cerdelga	eliglustat	04/12/2007	21/01/2015	Treatment of Gaucher Disease
Holoclar	ex-vivo expanded autologous human corneal epithelium containing stem cells	07/11/2008	19/02/2015	Treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns
Lenvima	lenvatinib	26/04/2013	01/06/2015	Treatment of follicular thyroid cancer
Hetlioz	tasimelteon	23/02/2011	07/07/2015	Treatment of non-24-hour sleep-wake disorders in blind people with no light perception
Unituxin	chimeric monoclonal antibody against gd2	21/06/2011	18/08/2015	Treatment of neuroblastoma
Kanuma	sebelipase alfa	17/12/2010	01/09/2015	Treatment of lysosomal acid lipase deficiency
Farydak	panobinostat	08/11/2012	01/09/2015	Treatment of multiple myeloma
Strensiq	recombinant human tissue non-specific alkaline phosphatase - fc - deca-aspartate fusion protein	03/12/2008	01/09/2015	Treatment of hypophosphatasia
Raxone	ibedenone	15/02/2007	10/09/2015	Treatment of Leber's hereditary optic neuropathy
Cresemba	isavuconazole	04/07/2014	19/10/2015	Treatment of invasive aspergillosis
Blincyto	blinatumomab	24/07/2009	25/11/2015	Treatment of acute lymphoblastic leukaemia
Kyprolis	carfilzomib	03/06/2008	23/11/2015	Treatment of multiple myeloma
Blincyto	blinatumomab	24/07/2009	25/11/2015	Treatment of precursor cell lymphoblastic leukemialymphoma
Ravicti	glycerol phenylbutyrate	10/06/2010	01/12/2015	Treatment of inborn urea cycle disorders
2016				
Coagadex	human coagulation factor x	17/09/2007	18/03/2016	Treatment of hereditary factor X deficiency
Wakix	pitolisant	10/07/2007	04/04/2016	Treatment of narcolepsy

2.2 Legal Framework and orphan drug designation application in the USA

Rare diseases collectively affect 30 millions of USA citizens. These are often serious or life-threatening diseases and yet there are only about 400 drugs currently approved for rare diseases [12].

In the USA, as a result of advocacy from public and special interest groups in the late 1970s, the Orphan Drug Act (ODA) of 1983 was signed into law to provide several incentives to encourage biotechnology and pharmaceutical companies to develop orphan drugs for individuals with rare and neglected diseases [50].

Orphan drugs are used in diseases or circumstances which occur so infrequently in the USA, that there is no reasonable expectation that the cost of developing and making available a drug for such disease or condition will be recovered from sales in the USA for such drugs [51].

The ODA empowered the FDA to review and approve requests for orphan drug status, coordinate drug development, and award research grants. Although the initial legislation permitted manufacturers to apply for orphan product designation at any time, a 1988 amendment required sponsors to apply for orphan designation before submitting applications for marketing approval [52].

The 1992 amendment provides that if the drug is theoretically similar to an orphan drug authorised for the same rare disease, the applicant must demonstrate the clinical superiority of this drug, which is then considered in the same way as a new active ingredient.

Afterwards, in June 2013, FDA finalized changes to the Orphan Drug Regulation, clarifying the potential of using a single drug for multiple indications that would cause the total patient population to be > 200,000, but maintaining orphan drug status for a 'subset' of a disease where each patient population is < 200,000 [53]. An orphan subset means the use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug [54].

In the USA, the concept of 'orphan drug' does not simply cover pharmaceutical or biological products. It also covers medical devices and dietary or diet products. FDA created the Office of Orphan Product Development (OOPD) to help manage this regulatory function which assists potential sponsors of orphan products by directing the following programs [55]:

- Orphan Drug Designation Program – qualifies a product for special financial incentives;
- Orphan Products Grant Program – provides funding for clinical investigations;
- Paediatric Device Consortia (PDC) Grant Program – facilitates paediatric medical device development;
- Humanitarian Use Device (HUD) Program – motivates businesses to develop medical devices for rare diseases and conditions.

Orphan Drug Designation and Marketing Authorisation Application of the drug product are two necessary stages to be approved before an Orphan Drug can be marketed and each decision is regulated by different committees within the FDA (Figure 7) [56].

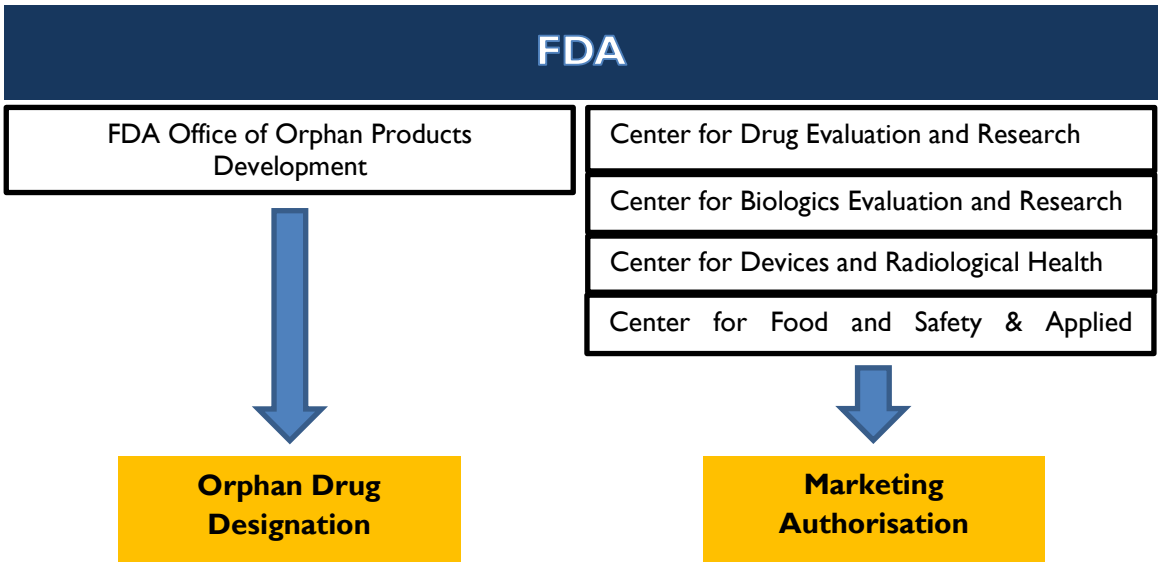


Figure 7. FDA committees which are responsible on the ODD and Marketing Authorisation procedures in USA

Adapted from [56].

2.2.1 Orphan Medicinal Product Designation in the USA

The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the USA, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing the drug [55]. A sponsor may request orphan drug designation of a previously unapproved drug, or of a new use for an already marketed drug [54].

A sponsor seeking orphan drug designation (ODD) for a drug must submit a request to the OOPD. For a drug to qualify for orphan designation both the drug and the disease or condition must meet certain criteria which are specified in the ODA. When preparing the application, the sponsor should give a particular focus to the following points [51]:

a) What is the disease?

A description of the rare disease or condition for which the drug is being or will be investigated, the proposed use of the drug, and the reasons why such therapy is needed.

b) Scientific Rationale Criteria: Is there "promise" that your drug will treat it?

A description of the drug and clinical experience with the drug in the rare disease or condition that are available to the sponsor, whether positive, negative, or inconclusive should be provided.

c) Prevalence Criteria: Is the disease rare?

Prevalence is defined as the number of persons who have been diagnosed as having the disease or condition at the time of the submission of the request for ODD; The number of people affected by the disease or condition for which the drug is to be developed has to be less than 200,000 persons.

d) Clinical Superiority: Is your drug the same drug as one already approved for the same disease indication?

If it is the same drug as an already approved drug for the same rare disease or condition, with or without orphan exclusivity, designation would be inappropriate. A sponsor should

explain why is clinically superior to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug).

In order to determine whether a drug qualifies as an OMP, the submitted application is reviewed by the scientific staff of the OOPD. After the receipt of the application, the assigned OOPD reviewer completes the assessment by preparing a review. This is followed by a second (OOPD team leader) and third level (OOPD Office Director) review. Following a positive decision, the sponsors' name, name of the drug and proposed indication are published. The typical review cycle is 90 days [18].

OD designations data compiled from the FDA OD Product designation database showed that, since 1984 until May 2015, the number of OD designations per year is continuously growing (Figure 8) [15].

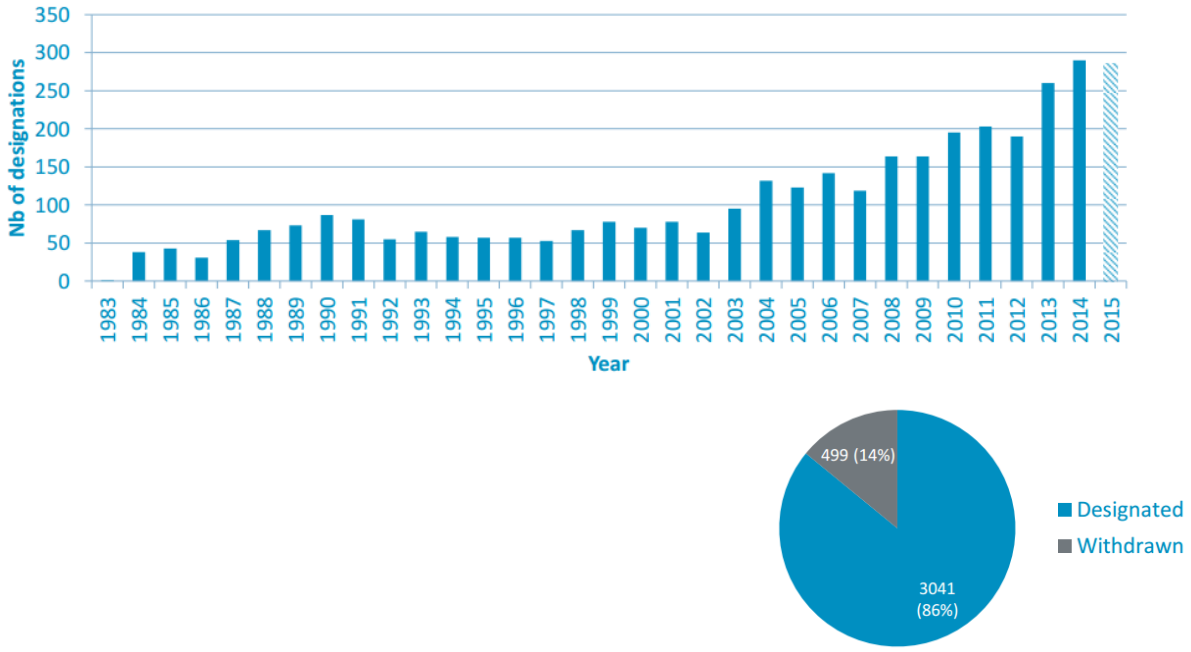


Figure 8. OD designations in FDA since 1984 until May 2015
Reproduced from [15].

Orphan designation qualifies the sponsor of the drug to receive some or all of the following incentives [56]:

i. Tax credit on clinical research

A sponsor may claim as tax credits half of the qualified clinical research costs for a designated orphan product [57].

ii. Fast-track procedure

Priority review of new drug applications (a 6-month review rather than the standard 10-month review). Fast Track speeds new drug development and review, for instance, by increasing the level of communication FDA allocates to drug developers and by enabling Center for Drug Evaluation and Research (CDER) to review portions of a drug application ahead of the submission of the complete application [58].

iii. Rare Pediatric Disease Vouchers

The Rare Pediatric Disease Priority Review Voucher Program was created under the FDA Safety and Innovations Act (FDASIA) to encourage development of drugs and biologics for rare pediatric diseases [59].

iv. Waiver of Prescription Drug User Fees

The sponsor's fee as prescribed by the Prescription Drug User Fee Act (PDUFA Fees) at the time of submitting a MA application to FDA are waived for a designated orphan product [57].

v. Marketing exclusivity

The first sponsor of a designated orphan drug to obtain FDA marketing approval for the designated rare disease or condition receives 7 years of marketing exclusivity [57]. More than one sponsor can receive an orphan designation for the same drug/indication. However, only the first drug to be approved for a given indication will enjoy the benefits of orphan approval. A product with a different active moiety can also receive orphan approval for an already approved orphan indication. Additionally, a second sponsor may gain orphan approval for a previously approved orphan drug/indication if the second sponsor's product demonstrates increased clinical benefit [60].

2.2.2 Post-Orphan Medicinal Product Designation

Within 14 months after the date on which a drug was designated as an orphan drug and annually thereafter until marketing approval, the sponsor shall submit a brief progress report to the FDA Office of Orphan Products Development [61].

After receiving the orphan designation and conducting more research, a sponsor may seek marketing approval if the drug proves safe and effective in clinical trials. The granting of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval [54]: Marketing Approval of a new drug filed under section 505(b) of the Federal Food, Drug, and Cosmetic Act and Marketing Approval of a biologics license submitted under section 351 of the Public Health Service Act [62].

In the USA, since 1983 until May 2015, 504 (14%) drugs with OD designation have received MA and 4 approvals have been subsequently withdrawn (Figure 9).

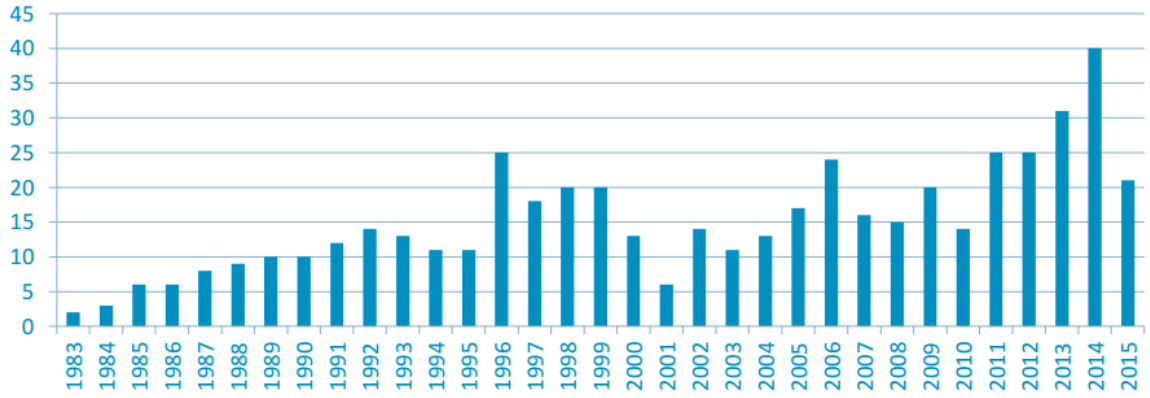


Figure 9. Number of OD that received Marketing Authorisation in USA
Reproduced from [20].

In 2015, CDER approved 45 novel drugs, as new molecular entities (NMEs) under New Drug Applications (NDAs) or as new therapeutic biologics under Biologics License Applications (BLAs). About 47% of the novel drugs approved in 2015 (21 of 45) were approved to treat rare or "orphan" diseases [58]. This is a noteworthy fact, given that over the last five years an average of just over 35% of FDA new drugs approvals each year were for rare diseases [63]. In Table 3 are listed the Orphan Medicinal Products that received Marketing Authorisation in 2015.

Table 3. CDER's Novel Drug Approvals in 2015, which were previously granted with orphan drug designation

Adapted from [58, 64].

Drug Name	Active Ingredient	Orphan Designation Date	Marketing Authorisation Date	Approved indication
Alecensa	alectinib	27/01/2015	11/12/2015	To treat ALK-positive lung cancer
Cholbam	cholic acid	18/07/2003	17/03/2015	Treatment of inborn errors of cholesterol and bile acid synthesis and metabolism
Cotellic	cobimetinib	31/01/2014	10/11/2015	Treatment of stage IIb, IIc, III, and IV melanoma with BRAFV600 mutation
Cresemba	isavuconazonium sulfate	25/10/2013	06/03/2015	To treat adults with invasive mucormycosis, rare but serious infections
		05/06/2013	06/03/2015	To treat adults with invasive aspergillosis, rare but serious infections
Darzalex*	daratumumab	05/06/2013	16/11/2015	To treat patients with multiple myeloma who have received at least three prior treatments
Empliciti*	elotuzumab	01/09/2011	30/11/2015	To treat people with multiple myeloma who have received one to three prior medications
Farydak	panobinostat	20/08/2012	23/02/2015	To treat patients with multiple myeloma
Kanuma*	sebelipase alfa	01/07/2010	08/12/2015	To treat patients with a rare disease known as lysosomal acid lipase (LAL) deficiency
Lenvima	lenvatinib	27/12/2012	13/02/2015	Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine refractory differentiated thyroid cancer
Natpara	parathyroid horomone	31/08/2007	23/01/2015	To control hypocalcemia (low blood calcium levels) in patients with hypoparathyroidism
Ninlaro	ixazomib	18/02/2011	20/11/2015	To treat people with multiple myeloma who have received at least one prior therapy
Orkambi *	lumacaftor / ivacaftor	30/06/2014	02/07/2015	To treat cystic fibrosis
Portrazza	necitumumab	20/11/2015	24/11/2015	To treat patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) who have not previously received medication specifically for treating their advanced lung cancer
Praxbind*	idarucizumab	28/05/2015	16/10/2015	For use in patients who are taking the anticoagulant Pradaxa (dabigatran) during emergency situations when there is a need to reverse Pradaxa's blood-thinning effects
Repatha	evolocumab	12/09/2013	27/08/2015	To treat certain patients with high cholesterol
Strensiq	asfotase alfa	12/09/2008	23/10/2015	To treat perinatal, infantile and juvenile-onset hypophosphatasia (HPP)
Tagrisso	osimertinib	04/09/2014	13/11/2015	To treat certain patients with non-small cell lung cancer
Unituxin*	dinutuximab	20/12/2010	10/03/2015	To treat pediatric patients with high-risk neuroblastoma
Uptravi	selexipag	30/04/2010	22/12/2015	To treat pulmonary arterial hypertension
Xuriden*	uridine triacetate	09/08/2013	09/04/2015	To treat patients with hereditary orotic aciduria
Yondelis	trabectedin	29/03/2005	23/10/2015	To treat specific soft tissue sarcomas (STS) – liposarcoma and leiomyosarcoma

** Orphan Drug approved as First-in-Class (i.e., with a new mechanism of action), one indicator of the innovative nature of a drug.*

The Orphan Drug Act (ODA) has been a great success, as demonstrated by more than 500 orphan drugs approved since its passage, with 233 of those approvals in the last decade alone. In contrast, the FDA had approved fewer than 10 orphan drugs in all of the 1970s before the ODA was passed. Moreover, research demonstrates that most of the recent approvals have been for diseases with fewer than 10,000 patients demonstrating the research community's commitment to meeting the needs of small patient populations [63].

2.3 Common EMA/FDA Application for Orphan Medicinal Product Designation

In 2007, a joint application form for orphan drug submissions in the USA and the EU was introduced, reducing the sponsor's administrative burden and encouraging parallel submissions to both agencies. The agencies have worked together to understand areas of similarity at the time of submission for an orphan drug designation, enhancing the understanding of key assessment criteria, which are similar in both systems [17].

The final goal is to facilitate development and marketing in different jurisdictions by setting a more fluid communication, closer collaboration, administrative simplification and mutual understanding to achieve finally as much voluntary harmonisation as possible [21].

The common application format allow sponsors to apply to both jurisdictions at the same time with one application and also establish a favorable environment for the EMA and FDA to share common experiences and gain an understanding of the similarities and differences of the process of obtaining orphan designation in the two regulatory systems [65].

By parallel submissions it is meant that a sponsor submits an application simultaneously to each agency. One of the key outcomes of this effort was the production of a joint application form [66]. However, the sponsor should take into consideration the key differences between orphan drug criteria in the EU and the USA [18].

This collaboration has already succeeded in delivering harmonised deadlines and content for the submission of annual reports on orphan medicine development, in agreeing a common format for applications for orphan designation, and in organising joint workshops aimed at pharmaceutical companies and patient's organisations on how to prepare an application for orphan designation [21].

Currently, it has been noted that approximately 50% of submissions to the EMA are done in parallel with the FDA, with 30–40% of applicants using the joint FDA–EMA application form. Although the review processes are done independently, most sponsors obtain their respective orphan designation in both regions within a maximum of 6 months of each other [17].

2.4 Legal Framework and orphan drug designation application in Japan

In 1972, the Ministry of Health and Welfare (MHLW) enacted the "General Outlines for taking Measures to deal with Intractable Disease [NAMBYO]" which was the first established in the world [67]. Originally, rare diseases were known as "intractable diseases (Nambyo)" in Japan.

Since then, measures to combat intractable diseases in Japan have progressed substantially, including : i) the "Specified Disease Treatment Research Program" established in 1972 with the support of the MHLW to promote research on 130 intractable diseases; ii) the revised "Orphan Drug Regulation" enacted in 1993 to encourage discovery and development of orphan drugs with specific incentives; iii) the "Intractable Disease Information Center" established in 1997 to provide vast information to patients with intractable diseases, and iv) designation of "Bases for Early and Exploratory Clinical Trials in Specific Research Areas" starting in 2011 to promote the development of innovative drugs and medical devices originating from Japan. Furthermore, "Revision of Measures to Combat Intractable Diseases" was approved in January 2013 in order to promote measures to combat intractable diseases in light of changing social and financial resources [68].

In Japan, drugs and medical devices can be designated as orphan drugs or medical devices based on the Article 77-2 if they fulfill the following criteria [69]:

1. Number of patients

The number of patients who may use the drug should be less than 50,000 in Japan (less than 3.9 per 10,000 individuals approximately).

2. High priority in health care needs

The drugs should be indicated for the treatment of serious diseases, including difficult-to-treat diseases. In addition, they must be drugs for which there are high medical needs satisfying one of the following criteria: there is no appropriate alternative drug or treatment in Japan and high efficacy or safety is expected compared with existing medical products in Japan [70].

3. High possibility of development

There should be a theoretical rationale for the use of the product for the target disease, and the development plan should be appropriate [70].

Orphan designation in Japan also affords a company with certain services that may be provided by the MHLW or by the Pharmaceuticals and Medical Device Agency (PMDA) and by the National Institute of Biochemical Innovation (NIBIO). When requested for guidance and advice to support the development of an Orphan product, the MHLW, PMDA or NIBIO, can provide significant resources and support to organizations developing these products for rare disease. The responsibilities of major regulatory authorities involved in the designation system in Japan are described in Figure 10 [69].

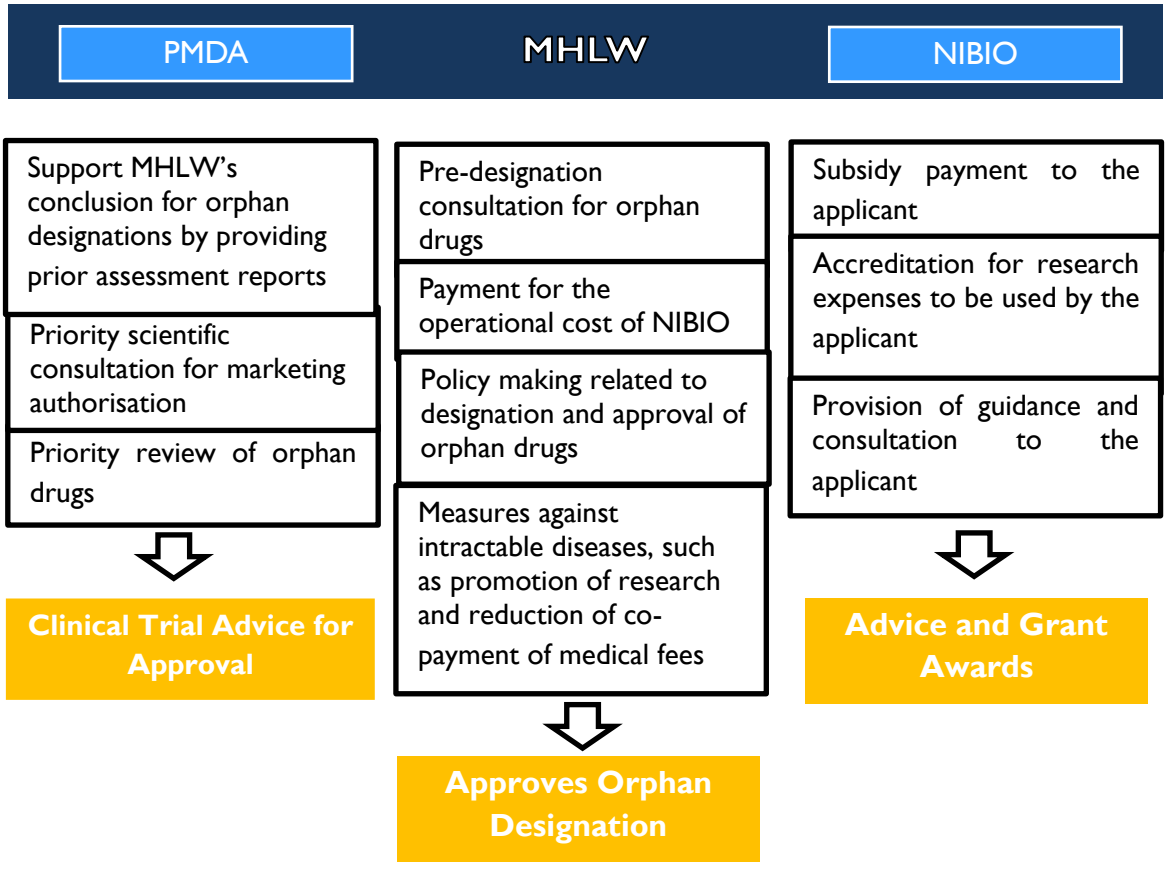


Figure 10. Regulatory authorities involved in the orphan designation system in Japan
Adapted from [69].

2.4.1 Orphan Medicinal Product Designation in Japan

To obtain a designation as an Orphan product in Japan, the sponsor initially submits a predetermined application form and summary information to demonstrate that the product meets the criteria to treat a rare disease [69].

This application is filed to the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau at the MHLW [69]. The application should contain the following information [71]:

- estimated size of the patient population in Japan for whom the product is intended;
- supporting information in terms of medical need;
- available data at the time of application;
- development plan.

The MHLW will evaluate the application and may request more information as needed, or request a meeting with the sponsor. The MHLW may also request advice from the Pharmaceutical Affairs and Food Sanitation Council on the indication and qualification as a rare disease in Japan. Given the requirements for designation as an Orphan Medicinal Product, it is important also for the sponsor to present a strong rationale and potentially proof of principle data in animals or humans that the product has a high potential to treat the rare disease [69].

The Japanese government's support for research and development of orphan drugs can be classified at two levels (administrative and financial) [72]:

- **The administrative level**

a. Subsidy payment

Orphan drug/medical device applicants can receive subsidies through the National Institute of Biomedical Innovation (NIBIO) to reduce the financial burden of product development. The total budget in the year 2010 was 650 million yen.

b. Guidance and consultation

Orphan drug/medical device applicants can receive guidance and consultation from the Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA), and NIBIO on research and development activities. PMDA provides a priority consultation system for designated orphan drug/medical device. Lower user fee categories for PMDA's consultation are applicable to designated orphan drugs.

c. Preferential tax treatment

12% of study expenses for orphan drug/medical device incurred during the NIBIO subsidy payment period (not including subsidies granted by NIBIO) can be reported as a tax credit.

d. Priority review

Designated orphan drugs and medical devices will be subject to priority review for marketing authorisation to ensure that they are supplied to clinical settings at the earliest possible opportunity.

e. Extension of re-examination period

After orphan drug/medical device designation and approval, the re-examination period for the drugs will be extended up to 10 years for drugs and up to 7 years for medical devices.

- **The financial level**

a. Research and development (R&D) grants for development of orphan products:

The NIBIO offers grants for the development of orphan products up to 50% of the R&D cost.

b. Tax reduction or credits:

Tax credits are granted for 12% of the drug's development cost, after subtracting any NIBIO grant. NIBIO provides consultation for companies regarding tax deduction.

c. Fees associated with Marketing Authorisation application:

A 25% reduction in initial regulatory user fees for review of the marketing application is granted.

The National Institute of Biomedical Innovation, Health and Nutrition database provide information concerning the OD designation requested in Japan. It can be seen in Figure 11 that the number of OD designations was low between 2001 and 2010, but as significantly improved in the last few years.

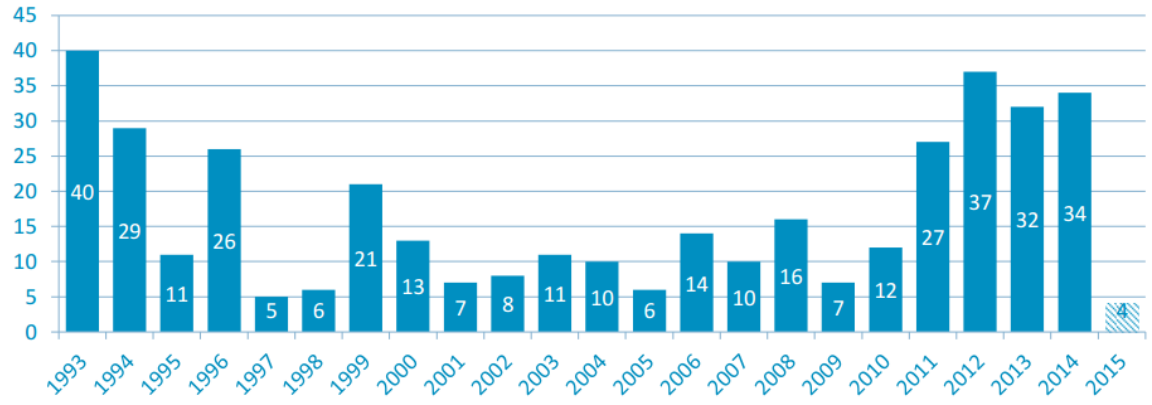


Figure 11. OD designations granted in Japan until May 2015
Reproduced from [15].

2.4.2 Post-Orphan Medicinal Product Designation in Japan

The information about designation and approval of orphan drugs and orphan medical devices are publicly available on NIBIO's website. After orphan drug designation, the PMDA offers consultation services regarding protocol development of studies for marketing approval (applicants with orphan products are given priority over applications for non-orphan products) and decides the amount of data required to support marketing approval on a case-by-case basis. NIBIO provides advice regarding studies carried out during this period [71]. Since 1994 from May 2015, 246 (64%) designated ODs have received marketing authorisation (Figure 12).

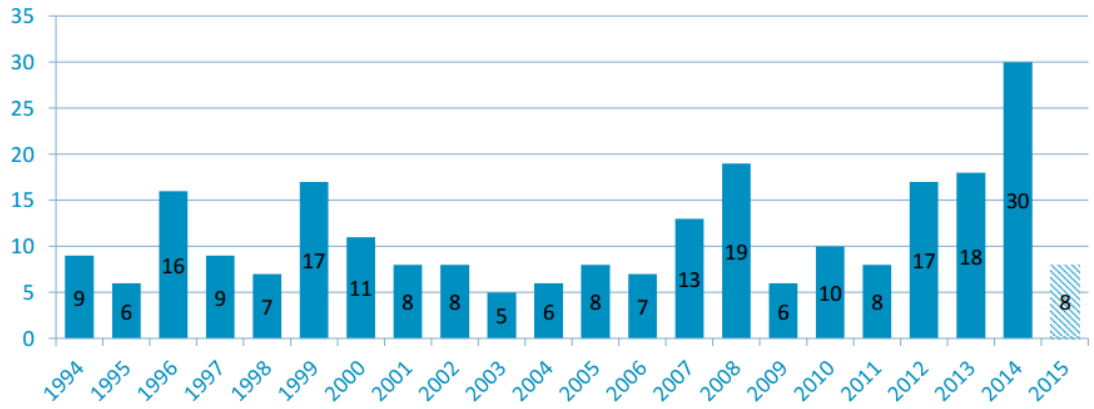


Figure 12. Number of OD that received Marketing Authorisation in Japan until May 2015
Reproduced from [15].

Additionally, the Orphan Medicinal Products approved in Japan since 2015 until April 2016 are listed in Table 4.

Table 4. New Orphan Drugs that received Marketing Authorisation in Japan in 2015 and until April 2016
Adapted from [73, 74].

Drug Name	Active Ingredient	Orphan Designation Date	Marketing Authorisation Date	Approved indication
2015				
Aldreb for Injection	colistin sodium methanesulfonate	10/11/2013	26/03/2015	Treatment of infections caused by colistinsensitive Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Pseudomonas aeruginosa, and Acinetobacter (limited to the strains resistant to other antimicrobial drugs)
Cerdelga Capsule	eliglustat tartrate	09/03/2011	26/03/2015	Improvement of various symptoms of Gaucher disease (anemia, thrombocytopenia, hepatosplenomegaly, and bone disease)
Lenvima Capsule	lenvatinib mesilate	16/08/2012	26/03/2015	Treatment of unresectable thyroid cancer
Pomalyst Capsules	pomalidomide	11/06/2014	26/03/2015	Treatment of relapsed or refractory multiple myeloma
Triumeq Combination	dolutegravir sodium, Abacavir sulfate, Lamivudine	13/09/2013	26/03/2015	Treatment of HIV infection
Cell Culture-derived Influenza Emulsion HA	cell culture-derived influenza emulsion HA vaccines	13/06/2012	26/03/2015	Prevention of pandemic influenza
NovoThirteen	catridecacog	13/05/2014	26/03/2015	Control of bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency
Laserphyrin	talaporfin sodium	17/03/2014	26/05/2015	Treatment of recurrent esophageal cancer associated with local persistence after chemoradiotherapy or radiotherapy
Pegintron	peginterferon alfa-2b	17/09/2014	26/05/2015	Adjuvant treatment of melanoma
Rituxan	pituximab	NA*	26/05/2015	Treatment of CD20-positive, B-cell non-Hodgkin's lymphoma
Velcade	bortezomib	NA*	26/06/2015	Treatment of patients with mantle cell lymphoma
Radicut	edaravone	NA*	26/06/2015	Delaying the functional disorder in patients with amyotrophic lateral sclerosis (ALS)
Ofev	nintedanib ethanesulfonate	NA*	03/07/2015	Treatment of idiopathic pulmonary fibrosis
Yervoy	ipilimumab	NA*	03/07/2015	Treatment of unresectable melanoma
Farydak	panobinostat lactate	NA*	03/07/2015	Treatment of relapsed or refractory multiple myeloma
Strensiq Subcutaneous Injection	asfotase alfa	NA*	03/07/2015	Treatment of hypophosphatasia
Tracleer Tablets	bosentan hydrate	NA*	24/08/2015	Inhibiting development of digital ulcer in patients with systemic scleroderma (only for patients who currently have digital ulcers or have a history of digital ulcer).

INOflo for Inhalation	nitric oxide	NA*	24/08/2015	Improvement of pulmonary hypertension in the perioperative period of cardiac surgery
Remicade	infliximab	NA*	24/08/2015	Treatment of entero-Behcet's disease, neuro-Behcet's disease, and vasculo Behcet's disease in patients who have not responded sufficiently to conventional therapies
Caprelsa	vandetanib	NA*	28/09/2015	Treatment of unresectable medullary thyroid cancer
Tracleer	bosentan hydrate	NA*	28/09/2015	Treatment of pulmonary arterial hypertension
Copaxone	glatiramer acetate	NA*	28/09/2015	Prevention of relapse in multiple sclerosis
Yondelis	trabectedin	NA*	28/09/2015	Treatment of patients with soft tissue sarcoma
Remicade	infliximab	NA*	21/12/2015	Treatment of acute-phase Kawasaki's disease in patients who have not responded sufficiently to conventional therapies
2016				
Bexarotene	bexarotene	NA*	22/01/2016	Treatment of cutaneous T-cell lymphoma

NA* – Not available. All these drugs obtained a designation as Orphan Product, however Orphan Designation Date was not available in literature.

2.5 Common EMA/Japan Application for Orphan Medicinal Product Designation

The EMA's collaboration with the MHLW/ PMDA began in late 2010 [17]. However, effective collaboration between the EMA and the MHLW-PMDA in the field of orphan medicines only was initiated in 2012. The agencies currently exchange information on the legal grounds, regulatory systems and operational aspects of orphan medicine development [75].

EC/EMA and MHLW/PMDA collaboration have implemented various measures to promote orphan medicine development. Under the confidentiality arrangements between the EC/EMA and MHLW/PMDA in the field of pharmaceutical affairs, exchanging experience and information would lead to improvement of measures taken by each authority in timely manner, as well as accumulation of supplement data, which would enable the balance between risk and benefit about orphan medicines to be evaluated in the comprehensive way [76].

This collaboration aims to create a greater mutual awareness of the submission processes for orphan medicine designations and the development of a system of exchange regarding the outcomes of orphan designations. However, due to the administrative differences between the EMA and the MHLW/PMDA (such as all submissions to Japanese authorities have to be submitted in Japanese), a common designation application form was not considered feasible yet [17].

In conclusion, the EMA and the MHLW/PMDA have worked together to establish greater clarity regarding each other's processes in the hope of encouraging parallel submissions and facilitating access to mutual incentive programs for orphan-designated products. An English website for the MHLW was developed, and the EMA Orphan Designation website has some links to the MHLW's website. One similarity between the Japanese and the European systems is the use of a committee of independent experts to make a recommendation for granting a designation [17].

2.6 Comparison of OD-based legislations in Europe, USA and Japan

Table 5 summarises all the information presented in the previous sections regarding regulatory aspects associated with orphan drug designation in the EU, USA and Japan.

Table 5. Summary of the orphan drug regulatory framework (requirements and benefits granted) in the EU, USA and Japan
Adapted from [18, 40].

	EU	USA	Japan
Authorities involved	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	FDA	Pmda JAPAN
Authorities involved	European Medicines Agency	Food and Drug Administration	Ministry of Health, Labour and Welfare
Bodies involved in designation procedure	EMA - COMP EC	FDA OOPD	MHLW PAFSC PMDA
Legal framework	Regulation (CE) N°141/2000 (2000)	Orphan Drug Act (1983)	Article 77-2 of the Pharmaceutical Affairs Law (1993)
Prevalence criteria	<5 in 10,000 patients	<200,000 patients	<50,000 patients
Review Period	Max. of 90-day procedure	Review cycle typically 90 days	None specified
Incentives			
Grants	Funding is available from the European Commission and other sources	Orphan Products Grants Program	Funding is available from National Institute of Biomedical Innovation (NIBIO)
Financial incentives	No general tax credit on clinical trials and no specific subsidies for clinical trials Regulatory fee reductions generally favour small and medium-sized enterprises, but are revised from time to time	Tax credits can apply to as much as 50% of qualified clinical development costs (USA studies) User fees paid to the FDA for review of the sponsors' application for marketing authorisation are waived	Financial subsidies for up to 50% of expenses for clinical and non-clinical research Subsidies through the NIBIO to reduce the financial burden of product development User fee waivers, 15% tax credits, up to 20% corporate tax reduction and a 30% reduction in marketing application fees
Marketing exclusivity	10-year market exclusivity (protects against a similar drug being authorized for the same therapeutic indication)	7-year marketing exclusivity (FDA cannot approve another marketing application for the 'same' drug treating the 'same' orphan diseases or conditions)	Extension of the re-examination period to 10 years at marketing authorisation
Scientific advice (protocol assistance)	Access to free-of-charge protocol assistance at the EMA for SME Guidance on the regulatory requirements regarding quality, non-clinical development and the design of the clinical trials necessary to fulfil the regulatory requirements for the demonstration of efficacy and safety of the drug	Access to free scientific guidance at the FDA Guidance by the relevant review division at the FDA on the regulatory requirements for quality, non-clinical development and the design of the clinical trials to demonstrate the efficacy and safety of the drug	A 30% fee reduction for protocol assistance Guidance is given on the regulatory requirements regarding quality and non-clinical development, as well as on the design of the clinical trials necessary to fulfil the regulatory requirements for marketing authorisation

	EU	USA	Japan
Grants for research programmes	The European Commission supports rare disease research through its framework programmes and the call for proposals in the rare disease area Member states offer a variety of grants	The FDA Orphan Products Grant Program offers funding for clinical studies (investigating safety and/or effectiveness) that will result in or substantially contribute to market approval The National Institutes of Health (NIH) also has a grants mechanism for rare diseases	Japanese National Health Insurance and pharmaceutical companies support measures include grants in aid for clinical and non-clinical research programs, price-control policies negotiated and medical expense reimbursement NIBIO and AMED offer grant programmes to SMEs and researchers who are developing products for rare diseases
Regulatory tools to accelerate approval of drugs	Fast-track approval Breakthrough designation Accelerated approval pathway Priority review designation	Priority medicines (PRIME) Centralized procedure Conditional approval Approval under exceptional circumstances Accelerated assessment	Priority review Fast-track approval

AMED, Agency for Medical Research and Development; FDA, US Food and Drug Administration; NIBIO, National Institute of Biomedical Innovation.

Chapter 3 - Pharmaceutical market: positioning of orphan drugs and focus on biotechnology-derived orphan drugs

3.1 Pharmaceutical market: general overview

3.1.1 Pharmaceutical market by therapy area

The Pharmaceutical industry's long successful strategy of placing big bets on a few molecules, promoting them heavily and turning them into blockbusters worked well for many years, but its R&D productivity has now plummeted and the environment's changing [77].

EvaluatePharma report [78] predicts that oncology will remain the largest segment in 2020 with an expected annual growth of 11.6% per year and reaching $US153.1 Bn in 2020. Anti-diabetics is forecast to be the second biggest therapy area with sales of $ 60.5 Bn in 2020, less than half that of oncology (Figure 13).

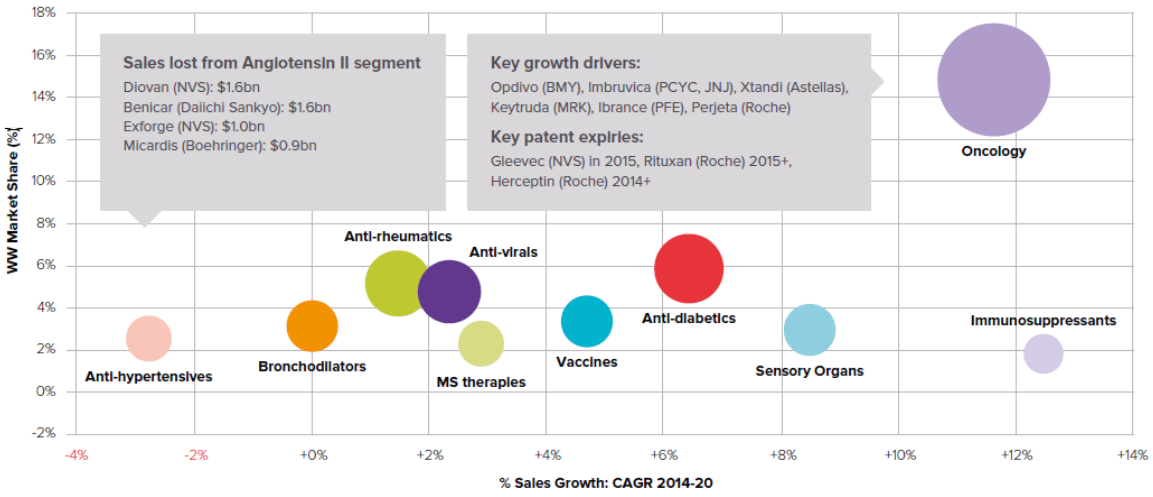


Figure 13. Worldwide Prescription Drug & OTC Sales by Therapy Area in 2020
Reproduced from [81].

3.1.2 Pharmaceutical market by type of drug developed

Biotechnology promises to revolutionize medicine and healthcare, using cutting-edge technology to develop techniques, treatments, and drugs to treat diseases and improve patients' quality of life. The biotech industry covers a wide range of companies and fields that use living systems and organisms to develop their products. These fields may include genetics and genetic engineering, cell and tissue sciences, gene therapy, applied immunology and bio-engineering [79].

EvaluatePharma Report [78] finds that, although the percentage sales from biotechnology products (bioengineered vaccines & biologics), within the world's top 100, is set to increase from 44% in 2014 to 46% in 2020, this is lower than the 52% predicted in their last year's World Preview Report. Concurrently, a number of conventional drugs, such as Celgene's Revlimid and Gilead's hepatitis C franchise, have had their forecasts upgraded, thereby increasing their contribution to the total value of the top 100 drugs in 2020. In the broader market, sales from biotechnology products are expected to account for 27% of the world's pharmaceutical sales by 2020 versus the share of 23% in 2014 (Figure 14).

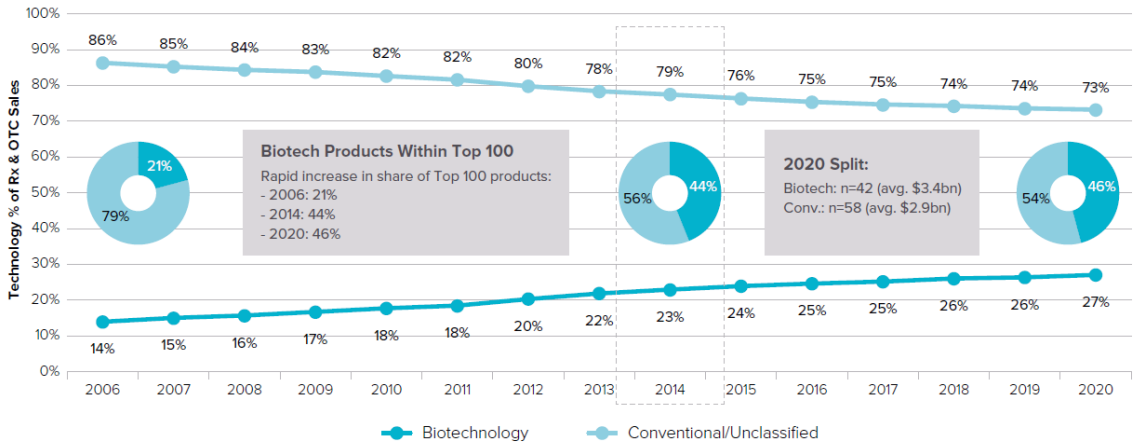


Figure 14. Worldwide Prescription Drug & OTC Pharmaceutical Sales: Biotech vs. Conventional Technology (2006-2020)
Reproduced from [78].

3.1.3 Pharmaceutical market: orphan drugs versus non-orphan drugs

The increased focus on rare diseases started in part because of the stimulus provided by the Orphan Drug Act (ODA) in the USA and similar Acts in other regions of the world [80].

The benefit of orphan versus non-orphan drugs is that orphan drugs are protected by additional exclusivities. Extended period of exclusivity for these drugs means that they are insulated from generic competition for a potentially longer period than their non-orphan counterparts. Orphan drug exclusivity does not have any association with patents, and may or may not give exclusivity beyond the composition of the matter patent [80].

EvaluatePharma report [19] predicts that the market for orphan drugs, based on the consensus forecast for the leading 500 pharmaceutical and biotechnology companies, will grow by 11.7% per year (CAGR) between 2015 and 2020 to $178 Bn (Figure 15). The growth of the orphan drug market is almost double that of the overall prescription drug market. Orphan drugs are set to account for 20.2% of global prescription sales in 2020, excluding generics, compared to 6.1% in 2000.

	WW Prescription Sales ($bn)														
Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
WW Orphan Drug Sales	44	51	60	63	70	79	84	90	97	102	114	129	145	161	178
WW Non-Orphan Drug Sales	458	502	537	549	557	584	566	564	576	559	578	602	634	666	701

Figure 15. Worldwide Orphan and Prescription Drug Sales (2006-2020)
Reproduced from [19].

3.2 Biotechnology providing powerful tools to diagnostics and treatments for orphan diseases

Biotechnology provides powerful tools to develop diagnostics and treatments for orphan diseases. With an estimated 5 new rare diseases identified every week, orphan drug development is becoming an increasingly important component of biopharmaceutical R&D. At least 80% of rare diseases have genetic origins, that is why medicines manufactured through biotechnology and gene technology can provide a valuable solution to treat rare diseases [81].

Particularly significant is that biopharmaceutical research is entering an exciting new era with a growing understanding of the human genome [81].

The sequencing of the human genome and the analysis of critical proteins in the blood have profoundly impacted biopharmaceutical research and are yielding important new tools for understanding and treating a wide range of conditions. These tools are proving critical for taking on rare diseases, which are often more complex than more common diseases. Many rare diseases will require new tactics to find effective treatments [82].

The exact cause for many rare diseases remains unknown. Still, for a significant portion, the problem can be traced to mutations (changes) in a single gene. Many of these genetic mutations can be passed on from one generation to the next, explaining why certain rare diseases run in families [83]. Thus, nucleic acids are highly promising candidates for the treatment of rare diseases. It is expected that not every nucleic acid approach will result in a therapeutic effect for every rare disease. In addition, many rare diseases are multi-system diseases which impact more than one organ or physiological process, so treatment using a singular therapeutic or delivery regimen may not be successful. Furthermore, the efficient and cell-specific delivery of oligonucleotide therapeutics remains a challenge for clinical progress [84].

Furthermore, orphan drug policies also represent an opportunity for biotechnology companies, especially those involved in the development of proteins, enzymes, and antibodies. The heavy dependence of most young pharmaceutical / biotechnology companies on private R&D investment funds ensures that the promise of some year exclusivity remains attractive.

A company that obtains orphan designation attracts interest from investors because of the clinical potential of the molecule being developed, the financial incentives accompanying the designation (grants, tax credits), and the regulatory support provided by the Authorities (e.g. Protocol Assistance). There are a few other factors that positively influence the economics of orphan drug development: timelines are typically shorter; more flexible pathway until marketing approval because of the lack of alternative treatments. Additionally, approved orphan drugs often require less marketing and are generally well reimbursed. All these considerations have made orphan drug development strategies increasingly popular within big pharma and venture capital investors and, thus, with biotech entrepreneurs [85].

From the 5000 designations totally attributed over the years, approximately 800 designations were common among the USA, EU, and/or Japan. The Table 6 and Table 7 show a quantitative review of all orphan drug designations and approvals since the implementation of orphan drug legislation in these three regions, by therapeutic classification (ATC code) and drug type, respectively [86].

As shown in Table 6, the following number of orphan designations were identified in each region: 3345 in the USA, 1146 in the EU, and 359 in Japan. Of these designations, marketing approval was given to 496 products in the USA, 87 in the EU, and 236 in Japan. Regarding therapeutic classification, ATC Code L (oncology and immunomodulatory drugs) accounted for 30 - 40% of total designations across the three regions and ATC Code J (infectious diseases) was significantly higher in Japan than in the USA or EU [86].

Table 6. Type of application and therapeutic classification of designated orphan drugs
Adapted from [89].

	USA	EU	Japan
Original data from agencies			
Data collection period	1983–Feb. 2015	2000–Feb. 2015	1993–Feb. 2015
Number of orphan drug designations	3345	1146	359
Number of marketing approvals of designated orphan drugs	496	87	236
Therapeutic classification (ATC code) (%)			
A (Alimentary tract and metabolism)	10.4	15.8	11.3
B (Blood and blood-forming organs)	7.0	5.7	7.4
C (Cardiovascular system)	3.5	3.3	5.5
D (Dermatological drugs)	1.7	1.7	0.3
G (Genitourinary system and reproductive hormones)	1.7	0.9	2.2
H (Systemic hormonal preparations, excluding reproductive hormones and insulin)	1.6	2.1	1.9
J (Anti-infective products for systemic use)	6.8	4.4	16.5
L (Antineoplastic and immunomodulating agents)	40.4	40.8	31.0
M (Musculoskeletal system)	3.7	4.9	3.6
N (Nervous system)	8.8	7.2	10.7
P (Antiparasitic products, insecticides, and repellents)	1.8	0.7	1.1
R (Respiratory system)	4.4	6.3	1.4
S (Sensory organs)	2.9	4.7	2.6
V (Various ATC structures)	4.2	1.7	2.7
Others	1.2	0.0	0.5
Total	100.00	100.	100.0

Table 7. Type of designated orphan drugs
Reproduced from [86].

Drug Type (%)	USA	EU	Japan
Small molecules	59.5	56.0	63.5
Biologics	27.3	25.5	31.0
Nucleic acids/vectors/cells/tissues	9.4	17.1	1.1
Vaccines	0.7	0.3	3.8
Others	3.2	1.0	0.5
Total	100.0	100.0	100.0

In the consulted literature [86], drug type was coded as small molecule, biologic, nucleic acid/vector/cell/tissue, vaccine, or others. Chemicals, amino acids, and small peptides (<100 amino acids in length) were coded as small molecules. Antibodies, fusion proteins, and high molecular-weight enzymes (>10 kDa) were coded as biologics. Plasmids and vectors were coded as vectors, cells as cells, and tissue products as tissues. Vaccines for infectious disease prophylaxis, such as influenza vaccine, were coded as vaccines.

In terms of drug type, small molecules accounted for up to approximately 60% of designations, in average. Vaccines were more prevalent in Japan than in the USA or EU. This difference is attributable to the Japan-specific scope for orphan designation that covers vaccines for unrealized infectious diseases, such as pandemics.

New modalities, such as nucleic acids, vectors, cells, and tissues, have steadily increased their prevalence in the USA and the EU, as shown in Figure 16. Cell and tissue products in particular were more dominant in the EU than in the USA and Japan because in Japan mesenchymal stem cell and adipose-derived stem cell alone were listed as orphan drugs in the original website data. Additional investigation identified limited designations for tissue or cell-sheet therapy, not as drugs but as medical devices, suggesting generally limited orphan designations for cell and tissue products in Japan (Table 7) [86].

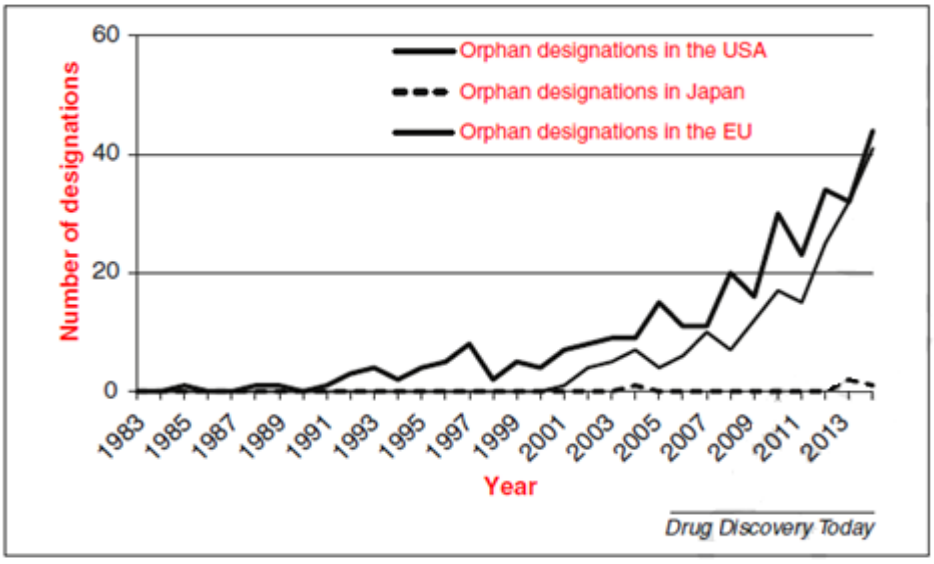


Figure 16. Number of orphan drug designations for new modalities (nucleic acid, vector, cell, and tissue products) over time in the USA, EU, and Japan
Reproduced from [89].

3.3 The top selling Orphan Drugs in the World

Whether the purpose is to license a drug, raise capital, or purchase stock on the open market, developing a dynamic and reliable forecast is the analyst's tool for determining the value drivers of a particular company [87].

At the same time, developing and gaining approval for new drugs has become more difficult. These factors mean big pharma needs to employ new strategies to maintain and grow business. This is done through a better assessment of the risk/return profile of drugs in their pipelines and outsourcing risk by partnering with biotechnology companies in need of their financial, technical, and marketing resources. Forecasting plays an essential role in determining which drugs will lead to the best returns and which drugs should be dropped before they consume too many resources [87].

Table 8 lists the top 20 of orphan drugs projected 2020 seller according to Thomson Reuters Cortellis™ Competitive Intelligence database. The Table 8 was originally elaborated for this thesis considering two different sources of information: Top 10 of Orphan New Molecular Entities approved in 2014 from EvaluatePharma 2015 report and Orphan New Molecular Entities approved in 2015 from FDA's Novel drugs 2015 Summary.

Revlimid is the world's expected best seller orphan drug in 2020, with sales of $10,891.08 M for all indications. The top 20 sellers of orphan drugs projected to 2020 includes chemical products as small molecules and products resulted from biotechnology with highlight for monoclonal antibodies (mAbs). Interestingly, novel drugs such as Repatha, Darzalex, Uptravi and Tagrisso which were approved in 2015 are included in this top 20, i.e. although recently approved their expected sales place them in the Top 20 of orphan drug most profitable.

Table 8. The Top 20 orphan drug brands by worldwide sales

Data collected from [58, 64, 88].

Rank	Product	Generic Name	Pharmaceutical Class	Biotech. Product?	**Forecast 2020 ($M)**	Regulatory status in the USA			
						Company	Orphan Designation Date	Marketing Authorisation Date	Approved Indication
1	Revlimid	lenalidomide	Immunomodulator	No	**10,891.08**	Celgene	27/04/2009	05/06/2013	Treatment of mantle cell lymphoma
							09/20/2001	17/02/2015	Treatment of multiple myeloma
							29/01/2004	27/12/2005	Treatment of myelodysplastic syndromes
							20/09/2001	29/06/2006	Treatment of multiple myeloma
2	Opdivo	nivolumab	Anti-programmed death-1 (PD-1) Mab	Yes	**10,178.78**	Bristol-Myers Squibb	07/08/2014	17/05/2016	Treatment of Hodgkin lymphoma
3	Keytruda	pembrolizu-mab	Anti-programmed death-1 (PD-1) MAb -	Yes	**5,161.14**	Merck & Co	19/11/2012	04/09/2014	Treatment of Stage IIB through IV malignant melanoma
							19/11/2012	18/12/2015	Treatment of Stage IIB through IV malignant melanoma
4	Rituxan	rituximab	Anti-CD20 MAb	Yes	**4,998.14**	Roche	13/06/1994	26/11/1997	Treatment of non-Hodgkin's B-cell lymphoma
							29/01/2004	18/02/2010	Treatment of chronic lymphocytic leukemia
							14/02/2006	19/04/2011	Treatment of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (Wegener's Granulomatosis, Microscopic Polyangiitis, and Churg-Strauss Syndrome)
5	Soliris	eculizumab	Anti-complement factor C5 MAb	Yes	**4,723.57**	Alexion Pharma-ceuticals	23/09/2011	23/09/2018	Treatment of atypical hemolytic uremic syndrome
							20/08/2003	16/03/2007	Treatment of paroxysmal nocturnal hemoglobinuria

Rank	Product	Generic Name	Pharmaceutical Class	Biotech. Product?	**Forecast 2020 ($M)**	Regulatory status in the USA			
						Company	Rank	Product	Generic Name
6	Imbruvica	ibrutinib	Bruton's tyrosine kinase (BTK) inhibitor	No	**4,423.75**	AbbVie (Pharmacyclics)	03/12/2012	13/11/2013	Treatment of mantle cell lymphoma
							06/04/2012	02/12/2014	Treatment of chronic lymphocytic leukemia (CLL)
							06/04/2012	28/07/2014	Treatment of chronic lymphocytic leukemia (CLL) with chronic lymphocytic leukemia with 17p deletion
							15/10/2013	29/01/2015	Treatment of Waldenstrom's macroglobulinemia
7					**3,242.75**	Johnson &Johnson (Janssen Biotech)	06/04/2012	04/03/2016	Treatment of chronic lymphocytic leukemia (CLL) without 17p deletion
							06/04/2012	28/07/2014	Treatment of chronic lymphocytic leukemia (CLL) with chronic lymphocytic leukemia with 17p deletion
							15/10/2013	29/01/2015	Treatment of Waldenstrom's macroglobulinemia
8	Orkambi	lumacaftor / ivacaftor	Cystic fibroses transmembranare conductance	No	**2,958.90**	Vertex	30/06/2014	07/02/2015	Treatment of cystic fibrosis
9	Repatha	evolocumab	Monoclonal antibody	Yes	**2,695.29**	Amgen	09/12/2013	08/27/2015	Treatment of homozygous familial hypercholesterolemia
10	Pomalyst	pomalidomide	Treatment of multiple myeloma	No	**2,384,91**	Celgene	15/01/2003	08/02/2013	Treatment of multiple myeloma
11	Tasigna	nilotinib	BCR-ABL tyrosine kinase inhibitor	No	**2,171.67**	Novartis Pharmaceuticals	27/04/2006	29/10/2007	Treatment of chronic myelogenous leukemia
12	Darzalex	daratumumab	Monoclonal antibody	Yes	**2,123.00**	Janssen Biotech	05/06/2013	16/11/2015	Treatment of multiple myeloma

Rank	Product	Generic Name	Pharmaceutical Class	Biotech. Product?	Forecast 2020 ($M)	Regulatory status in the USA			
						Company	Rank	Product	Generic Name
13	Gazyva	obinutuzumab	Monoclonal antibody against CD20	Yes	**1,990.30**	Genentech	17/02/2012	01/11/2013	Treatment of chronic lymphocytic leukemia
							15/04/2015	26/02/2016	Treatment of follicular lymphoma
14	Yervoy	ipilimumab	Monoclonal antibody	Yes	**1,878.25**	Bristol-Myers Squibb Company	03/06/2004	25/03/2011	Treatment of high risk Stage II, Stage III, and Stage IV melanoma
							06/03/2004	28/10/2015	Treatment of high risk Stage II, Stage III, and Stage IV melanoma
15	Esbriet	pirfenidone	Tumor necrosis factor alpha (TNF) transforming growth factor-beta inhibitor	No	**1,855.88**	Roche	05/03/2004	15/10/2014	Treatment of idiopathic pulmonary fibrosis
16	Kyprolis	carfilzomib	Proteasome inhibitors	No	**1,787.14**	Onyx Pharmaceuticals	18/01/2008	20/07/2012	Treatment of multiple myeloma
17	Sprycel	dasatinib	Protein kinase inhibitors	No	**1,646.00**	Bristol-Mayers – Squibb Company	18/11/2005	28/06/2006	Treatment of Philadelphia-positive acute lymphoblastic leukemia
							28/11/2005	28/06/2006	Treatment of chronic myelogenous leukemia
18	Alimta	pemetrexed disodium	Antifolate	No	**1,497.70**	Eli Lilly	28/08/2001	02/04/2004	Treatment of malignant pleural mesothelioma
19	Uptravi	selexipag	Prostacyclin receptor agonist	No	**1,467.59**	Actelion	03/04/2010	21/12/2015	Treatment of pulmonary arterial hypertension
20	Tagrisso	osimertinib	Kinase inhibitor	No	**1,445.79**	AstraZeneca Pharmaceuticals LP	04/09/2014	13/11/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer

Note: The new drugs approved in 2015 by the FDA (Repatha, Darzalex, Uptravi and Tagrisso), and which had previous orphan drug designation, are highlighted in color (light pink) in the present Table.

3.4 Case Study: Repatha® (evolocumab)

Evolocumab (Repatha®) is a fully human monoclonal antibody (mAb) administered subcutaneously and developed by Amgen. It has been approved as a treatment for two types of hypercholesterolaemia in the EU, USA and Japan, but only the FDA granted evolocumab an orphan drug designation for homozygous familial hypercholesterolemia (HoFH) (Table 9).

Table 9. Repatha's regulatory orphan status in the USA
Data adapted [64].

Disease	Date of ODD	Date of Marketing Authorisation	Approved Indication
Homozygous familial hypercholesterolemia (HoFH)	12/09/2013	27/08/2015	As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C

The main properties and characteristics of evolocumab are presented in Table 10.

Table 10. Features and properties of evolocumab
Adapted from [89].

Generic name	Evolocumab
Alternative codes / name	AMG 145; AMG-145; AMG145; Repatha
Class	Monoclonal-antibodies
Mechanism of action	PCSK9 protein inhibitor
Route of administration	Subcutaneous injection
Pharmacodynamics	Dose-dependently reduces mean LDL levels relative to placebo in healthy volunteers; marked reduction in free PCSK9 levels in patients with hypercholesterolaemia
Pharmacokinetics	Cmax mean (standard deviation [SD]) of 18.6 (7.3) μ g/mL AUClast mean (SD) of 188 (98.6) day• μ g/mL 8 weeks after a single 140 mg dose
WHO ATC code	C10A-X (other lipid modifying agents)
EphMRA ATC code	C10A9 (all other cholesterol/triglyceride regulators)
Sponsor	AMGen, Applied Molecular Genetics, Inc., California, USA

3.4.1 Therapeutic Indication

In 2015, the FDA approved evolocumab as an adjunct treatment to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. Only this indication (HoFH) is a rare disease and for that reason the following text focus on this disease [90].

Homozygous familial hypercholesterolaemia (HoFH)

HoFH is an inherited disorder of lipoprotein metabolism characterized by marked elevation of low density lipoprotein cholesterol (LDL-C), xanthomata and premature cardiovascular disease. In most cases the underlying genetic abnormality is mutation of both alleles of the LDL-receptor (LDLR) gene [91].

LDL is generated in the circulation by the delipidation and modification of very low density lipoproteins (VLDL) secreted by the liver. Apolipoprotein B100 (apoB100) is the major structural apoprotein of VLDL and LDL. LDL is cleared from the circulation by hepatic LDLR with apoB100 acting as the ligand for the receptor. The major pathophysiological abnormality in HoFH is decreased LDL clearance although hepatic overproduction of apoB100- 2 containing lipoproteins may further exacerbate the hyperlipidaemia [91].

The worldwide prevalence of HoFH is generally estimated to be one in a million while the prevalence of HeFH is estimated to be one in three- to five hundred, making the latter one of the commonest severe monogenic disorders in medical practice. The prevalence of HoFH is markedly increased in certain regions of the world and may be as high as one in thirty thousand in some populations [91]. HoFH is usually inherited in an autosomal co-dominant fashion but on occasions may also be inherited recessively. The HoFH phenotype may result from mutation of a single gene or more rarely may be the consequence of mutations in several different genes involved in lipoprotein metabolism. Currently four genes have been associated with the FH phenotype. All of these genes are critical to LDLR function and mutations result in impaired LDL clearance [91].

The proteins known to affect LDL receptor function and their role are summarized in Figure 17. Most patients with genetically confirmed HoFH have two mutant alleles of the LDLR gene (MIM 606945) and their parents each have HeFH. Recently, mutations in alleles of three other genes were identified as causal in some cases with a severe phenotype resembling HoFH. These secondary genes are APOB (MIM 107730) encoding apolipoprotein (apo) B, PCSK9 (MIM 607786) encoding proprotein convertase subtilisin/kexin type 9 (PCSK9), and LDLRAP1 (MIM 695747) encoding LDL receptor adapter protein 1, which uniquely causes a recessive phenotype, since carrier parents have normal lipid profiles [91].

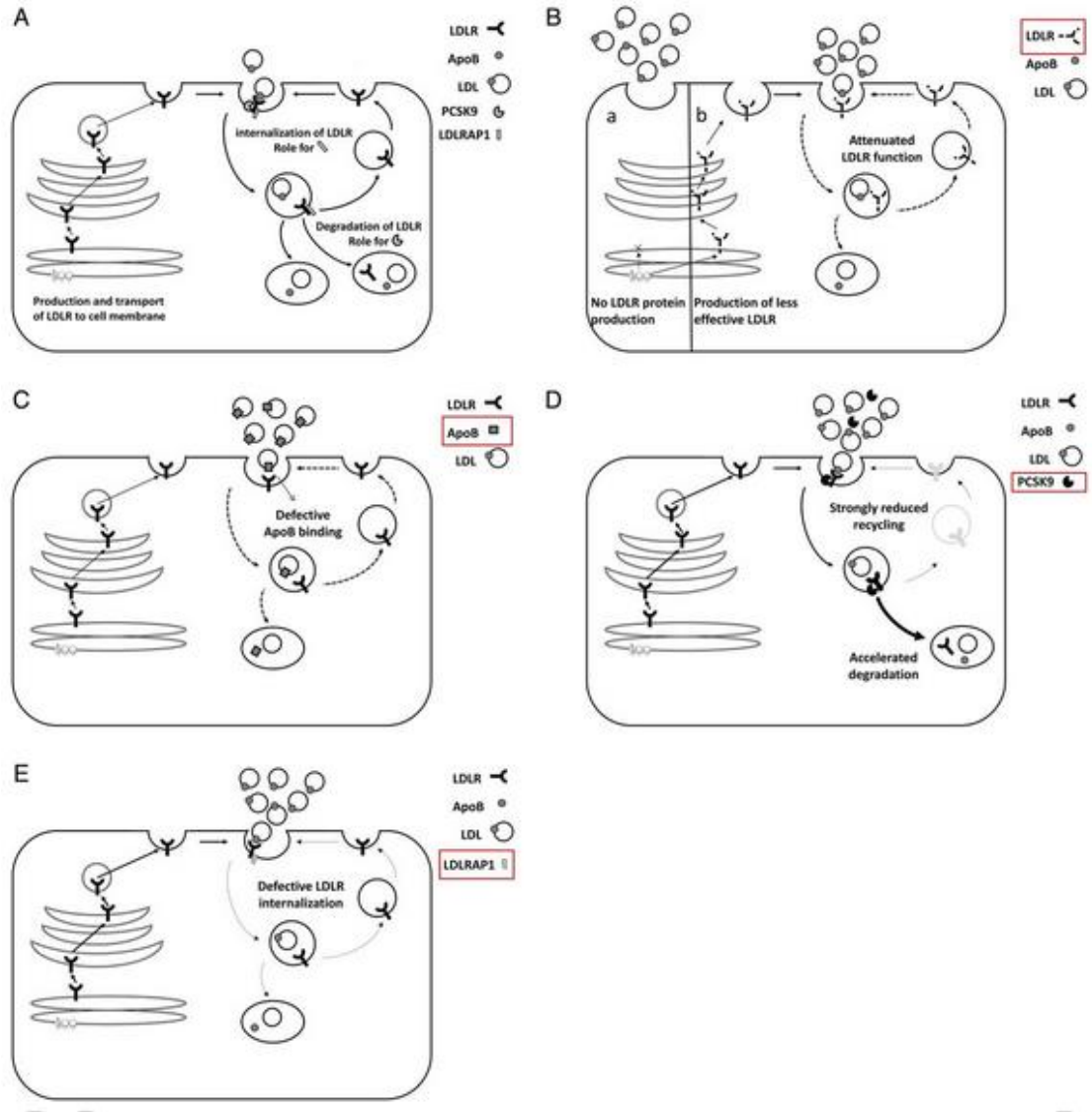


Figure 17. Proteins affecting low-density lipoprotein receptor (LDLR) function
Reproduced from [92].

3.4.2 Mechanism of action

Evolocumab is a human monoclonal immunoglobulin G (IgG2) directed against human protein convertase subtilisin kexin 9 (PCSK9). Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR, preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, evolocumab increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels (Figure 18) [89].

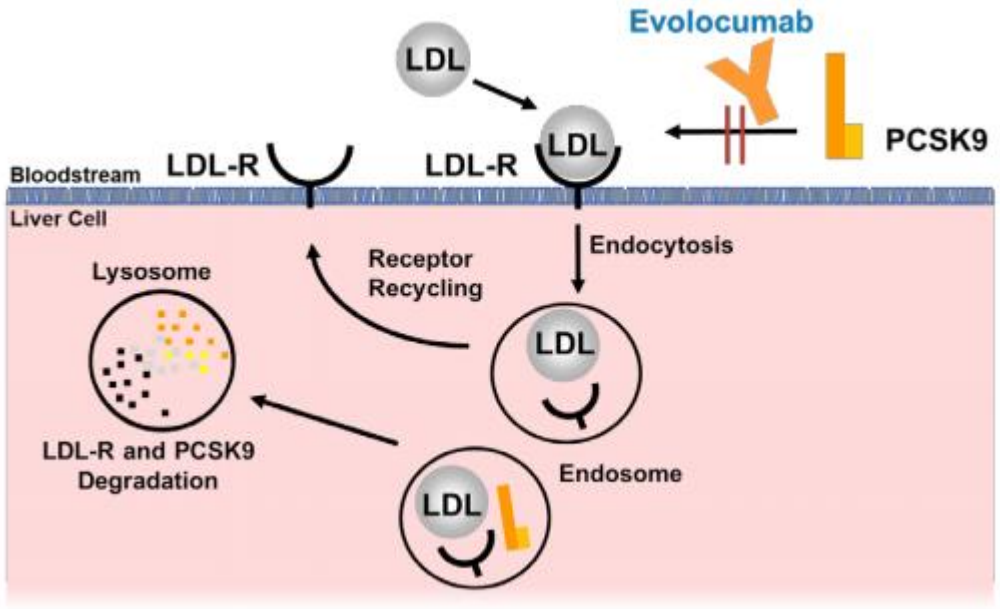


Figure 18. Mechanism of action for evolocumab
Reproduced from [93].

In addition to LDL-C lowering, inhibition of PCSK9 by evolocumab reduces total cholesterol, apolipoprotein B (ApoB), very low density lipoprotein cholesterol (VLDL C), triglycerides and lipoprotein(a) (Lp(a)), and increases HDL-c and ApoA1.

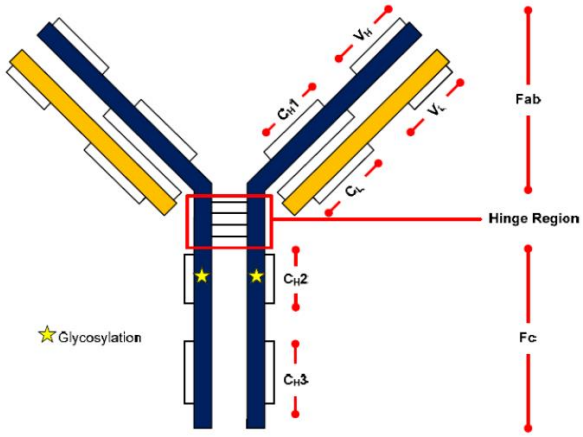
With its novel mechanism of action, evolocumab offers an addition to standard of care and available therapies in the reduction of LDL-C and improvements in other lipid parameters as a lipid-lowering agent. Based on these effects, evolocumab is being developed for use in the treatment of hyperlipidaemia and in particular in hypercholesterolaemia and mixed dyslipidaemia [89].

Evolocumab demonstrated a consistent and substantial beneficial effect on low density lipoprotein cholesterol (LDL-C) or "bad" cholesterol in several patient's groups (including patients at low cardiovascular risk, patients on maximum statin therapy, patients intolerant

to statins and HeFH patients) with hypercholesterolaemia and mixed dyslipidemia, as well as for HoFH patients on top of currently available therapies for LDL-C reduction. Evolocumab, administered every 2 weeks or every month, has an acceptable safety profile and is well tolerated, which is considered important for an intended life-long treatment [89].

3.4.3 Evolocumab drug substance

Evolocumab is a human monoclonal IgG2 antibody consisting of 2 heavy chains and 2 light chains of the lambda class (Figure 19). It contains 36 cysteine residues involved in both intrachain and interchain disulphide bonds. Each heavy chain contains 441 amino acids with 4 intrachain disulfides bonds while each light chain contains 215 amino acids with 2 intrachain disulfides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 291. Evolocumab does not involve Fc-region effector functions as a part of its mode of action, which occurs, in the binding and inhibition of PCSK9. Furthermore, human IgG2 isotype is known to have low affinity to Fc-γ receptors and C1q therefore having minimal immune effector functions [93].



Heavy chains are shown in blue and light chains are shown in orange
V_H is the variable domain of the heavy chain
C_H1, C_H2, and C_H3 are the constant domains of the heavy chain
V_L is the variable domain of the light chain
C_L is the constant domain of the light chain

Figure 19. The structure of evolocumab
Reproduced from [97].

The manufacture of evolocumab drug substance represents a conventional monoclonal antibody production process with the follow steps: fermentation, recovery, purification and viral inactivation. It is produced using this recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. Two cell banking systems, with a working cell bank (WCB) derived from the master cell bank (MCB) has been established and the identities and purities of the MCB and WCB have been evaluated in line with ICH Q5D [89].

All the manufacture process follows Quality by Design (QbD) principles and ICH Guideline Q11. There are adequate in-process controls and the manufacture is performed in accordance with the current Good Manufacturing Practices (GMP) [89].

Chapter 4 - Challenges during the development of Orphan Drugs: particular focus on clinical stage

4.1 Challenges of Orphan Drug Development

Before a potential new treatment can be approved, it must be tested in clinical trials. Advances in science and technology, such as personalized medicine, are creating new opportunities to improve and expand research into rare diseases and the development of new treatments [82].

Furthermore, there has been a rapidly-growing demand for clinical trials in orphan indications because of orphan drug legislation in both the USA and the EU that have established incentives to increase research in these areas. Public incentives and facilitations make drug development for rare diseases more financially viable [5].

In order to benefit from the regulatory and commercial incentives of orphan drug development, sponsors must be aware of the hurdles involved in studying rare diseases [94].

There are several requirements for a therapeutic study of human diseases: appropriate trial design and analysis to answer the research question, appropriate measurements to complement the trial design, selection of the correct sample, ethical recruitment to participation, funds to support the research, knowledgeable study staff, and adequate resources to execute the study and address regulatory concerns [95].

Clinical research in rare diseases faces evident obstacles, such as very or exceptionally low disease prevalence, small and heterogeneous patient populations, difficulty in recruiting such patients, disease severity, lack of or limited knowledge of disease natural history and high attrition rates during R&D processes [96]. Additionally, two thirds of rare diseases affect children primarily and half the current trials test innovative products, adding difficulties to the complexity of trial design and acceptability by regulatory authorities. On the other hand, randomized placebo-controlled clinical trials involving several hundreds of patients, which are typically part of drug development programmes for more common diseases may not be feasible in certain circumstances [95, 96]. This may occur in the area of rare diseases research, as well as in other areas, such as the pediatric population and in the stratification of more common diseases using biomarker data. Inherent to rare disease clinical research, small numbers of patients in clinical trials present certain challenges, in particular [97]:

- The total number of eligible subjects may be very limited, which impacts the choice of study design and the statistical methodology;
- Challenges in recruiting the necessary number of study subjects, where investigators may 'compete' for the same patient;
- Scarcity of expertise in some disease settings may impact on the ability to conduct the study in all geographical areas;
- The development programme may necessitate the coordination of numerous clinical study sites throughout the world;
- Even if the disease aetiology is known, lack of knowledge of the natural history of the disease may impact on the selection of the most appropriate endpoints;
- Smaller studies are more susceptible to the effects of variability;
- Missing data are likely to be more critical and have a greater impact on the conclusions;
- Greater vigilance is required to ensure that the publication of detailed clinical descriptions does not lead to subject identification.

The above mentioned difficulties will be described in more detail in the following sections.

4.1.1 Study Design & Execution Challenges

Clinical trials involving therapies for rare diseases are challenging for various reasons, including poor understanding of the natural history of the proposed indication due to few observational studies studying disease progression, heterogeneous patient populations with variable phenotypes and clinical courses, geographic dispersion of patients and investigators, regulatory uncertainties, lack of validated endpoints and lack of prior clinical studies to establish a template for study execution. In addition, small patient populations isolated in a few tertiary care centers go against traditional methods of study operation. Although these obstacles are not unique to orphan drug trials, the solutions to these challenges may be more difficult to find in these trials specifically.

When designing a clinical study focused on a rare disease, sponsors may find it difficult or impossible to find fundamental disease information, such as disease prevalence, incidence or treatment patterns, on which to base the study protocol. In most rare diseases, there are no standardized clinical trial designs or efficacy outcome measures, leading to difficulties in selecting appropriate endpoints, outcome measures, tools and biomarkers. The nature of rare diseases also makes it challenging to select appropriate study durations. Small patient

populations limit study variation and the genetic basis or associated co-morbidities of many rare diseases can be confounding factors in study predictability [94].

4.1.2 Recruitment Challenges

Recruitment for orphan drug trials is challenged by the small number of patients for each disease, low disease awareness in the general population and an ill-defined base of treating by the physicians or clinics [94].

The need to study patients at early stages for disease-modifying agents or, on the contrary, those at very advanced stages, when intervention risk is high, may not be feasible to narrow down entry criteria based on disease stage or other characteristics. Patients' geographical dispersion requires multicenter and multinational collaboration, introducing additional regulatory and funding obstacles. For severe rare diseases, travel to research centers may be impossible [98].

Selection criteria for orphan drug trials involves identifying countries with a sufficient number of suitable study participants, then determining whether these patients are accessible and willing to participate, and finally, identifying centers of excellence with the therapeutic and operational capabilities to execute the intended observational or interventional trial. The nature of the indication emphasizes the importance of the medical, cultural and regulatory context as well as the standard of care and treatment pathways within each country of interest for the clinical study [99].

Patient databases typically used as a recruitment resource are of limited utility in orphan indications because the primary inclusion criteria often consist of assessments that are not commonly recorded on medical charts. Patient recruitment may also be complicated by simultaneous studies of a rare disease, since enrollment in one trial may render a patient ineligible for another trial [94].

Additionally, many rare diseases are fatal in infancy or childhood and children who do survive to adulthood face difficulties transitioning from pediatric to adolescent to adult care, and frequently the clinical presentation will evolve. Understandably, patient recruitment, retention and management can present more challenges with a younger demographic group

of patients. Participants' physical, intellectual, and emotional growth, developing attitudes and beliefs, as well as family dynamics, all have an influence on their participation [99].

4.1.3 Regulatory Challenges

There are no documented differences in marketing approval criteria for orphan drugs and drugs for common indications, and sponsors must still prove substantial evidence of the effectiveness of the drug using adequate and well-controlled investigations. Nevertheless, the FDA has publicly expressed sensitivity to applying flexibility in its approval standards to new therapies for rare disorders. Additionally, EMA also provides guidance on procedures for the granting of marketing authorisation under exceptional circumstances, including indications which are encountered so rarely that comprehensive evidence cannot be provided, and orphan drugs may meet the criteria to be considered for approval under exceptional circumstances [94].

By working closely with regulatory authorities, the path to drug development and registration is highly individualized. Each situation is assessed on a case-by-case basis and deviations from a scientific "gold standard" may be acceptable. This is why clinical drug development in these cases should always be conducted based on extensive, thorough, pre-IND meeting or Scientific Advice with the authorities FDA and EMA, respectively [5].

4.1.4 Other Challenges

Other challenges associated with orphan drug development include ethical concerns and reimbursement scrutiny. A majority of rare diseases affect children, and pediatric studies require sponsors to carefully balance the ethical considerations of conducting studies in a vulnerable population with concerns about site selection, recruitment, compliance, and statistical powering. In children, the issue is not restricted solely to rare diseases as the difficulty in recruiting sufficient numbers of these patients is a problem for even frequent diseases. This difficulty is mainly due to ethical and psychological considerations, which not only represent an obstacle to running clinical trials but also to protecting the children [98].

With the growing number of orphan drugs on the market, the impact on payers is increasing and their attention towards orphan drug pricing and reimbursement is likely to increase, as well. Due to small market sizes, sponsors will need to develop a low-cost delivery model

that enables specialty pharmacies to provide orphan drugs to the patients who need them [98].

4.2 Innovative research methods for studying treatments for rare diseases

There are various strategies that sponsors can employ to plan for, and overcome, the clinical and regulatory challenges of orphan drug development.
High levels of evidence come from well-designed and well-executed clinical trials. In the small populations setting, the most appropriate trial approach will be determined on a case-by-case basis and will depend on the perceived advantages, the disadvantages and what may have to be sacrificed [97].

The objective of generating the best evidence base as possible in an ethical and timely manner can be achieved through rigorous planning and early engagement with the regulatory authorities, where discussions to ensure optimisation of the development programme can be fully explored and the acceptability of novel and innovative methodology can be prospectively agreed. This is the case of modelling and simulation, adaptive designs that permit flexibility to update various aspects of the study (including randomization scheme, number of treatment groups, and number and frequency of intermediate analyses) using pre-specified and statistically sound criteria [100].

For small rare disease populations, sponsors may have more success with clinical trial recruitment by reaching out to patients directly, rather than relying on investigators to identify qualified participants. Establishing an informational website and educational print materials targeted at patients and their caregivers may help with study recruitment. Sponsors should also consider working with patient support and patient advocacy groups / associations to drive clinical trial awareness to their members. Targeted advertising at the local level may be effective as well [94].

In order to enhance the clinical trial process for participants, as well as improve study outcomes, sponsors frequently utilize the experiences and knowledge of patients and caregivers in the process of trial design. By doing this, drug developers can gain valuable insight into experiences associated with a specific condition, after all, firsthand knowledge of

what it is like to progress through site visits and procedures while managing an illness is not something that can come readily, or exclusively, from a professional point of view [99].

A recent report published that, for new products entering Phase III trials from 1 January 2000, an average 761 patients were enrolled in orphan drug trials versus 3,549 in non-orphan drug trials [19]. Additionally, Table 11 also highlights that the cost of a phase III study with an orphan drug is, in average, approximately four times inferior to the cost of conducting a phase III with a non-orphan drug.

Table 11. Average Phase III Trials Sizes and costs (new drugs entering phase III from 1 Jan. 2000)
Adapted from [19].

Product Type	Phase III Trial Size					Phase III Cost ($m) Estimated		
	Median	Average	No. of Products (n=)	Total Patients	% of	Median	Average	Total
Orphan	538	761	466	354,705	10%	99	103	47,929
Non-Orphan	1,558	3,549	952	3,378,809	90%	150	193	189,543
All	921	2,633	1,418	3,733,514	100%	127	163	231,472

Although trial sizes showed in Table 11 are an average of all Phase III trials sizes considered, exceptional clinical development for a very rare disease can require trial sizes significantly different from the average for orphan drugs. As an example, FDA approved in 2015 an orphan drug based on the clinical results of a 4-patient trial. The FDA approved Wellstat Therapeutics' uridine triacetate (Xuriden®) for the treatment of hereditary orotic aciduria (HOA), an ultra-orphan indication that has been reported in only 20 people worldwide [101].

A sponsor company can obtain orphan designation status, at any stage of development, if it fulfils all criteria established by the regulatory authorities. The charts of Figure 20 are based on internal European Medicines Agency (EMA) data derived from the 1,406 applications for orphan designation that were granted a positive opinion by the Committee for Orphan Medicinal Products (COMP) and orphan designation by the European Commission between 2000–2014. The analysis of the stage of development of an orphan drug at the time of designation suggests that the majority of designations are based on clinical data (Figure 20.a). Nevertheless, a substantial percentage of applications comprise only preclinical data (Figure

20.a). The level of preclinical evidence in the applications that were submitted, shows that 86% of all submitted application includes both *in vivo* and *in vitro* data *(*Figure 20.b*)*.

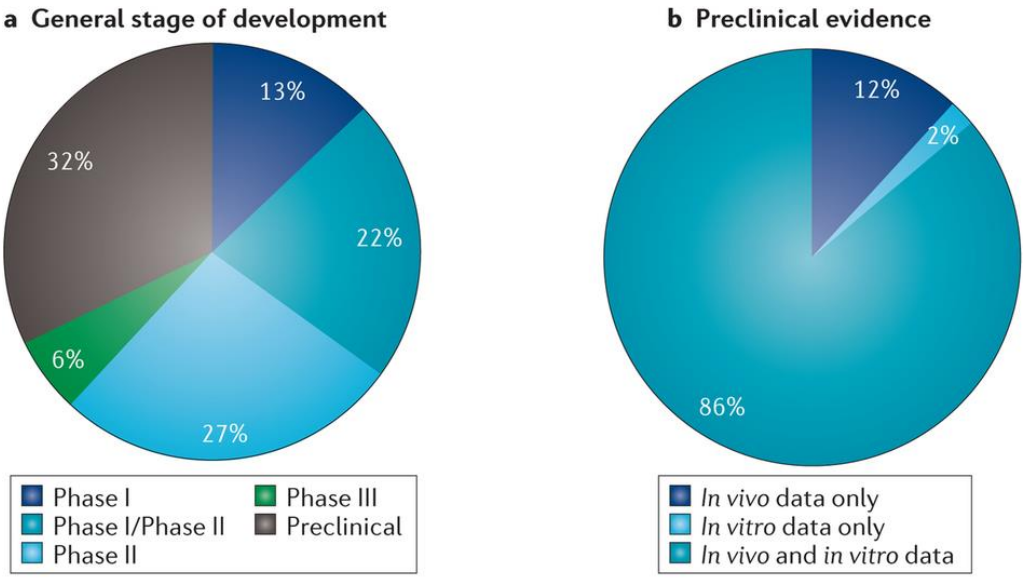


Figure 20. Information in applications for orphan drug designation in the European Union from 2000 to 2014
Reproduced from [17].

In recent years, innovative epidemiological and clinical trial methods have been developed that offer promise for promoting more efficient and effective research.

New methods have been proposed or used to analyze health outcomes in patients with rare disease in observational data. Some of these methods (for example, crossover designs and propensity scores) are already used in studies of common conditions. Awareness of the armamentarium of research tools available will help investigators design studies in patients with specific rare diseases and will help clinicians interpret the results of these studies when treating patients with these conditions. Observational studies are an important approach for studying health outcomes in rare diseases, particularly as patient registries and electronic healthcare databases continue to grow and offer richer clinical information [102].

In conclusion, as a result of innovative methods (exemplified in Table 12), the number of drugs that are successfully brought to market for a variety of orphan indications is likely to rise in the next years and decades. However, securing regulatory approval for the trial designs requires an exploration of innovation in study design, appreciation of evolving regulatory guidance, and incorporation of patient and family perspectives into the scope and detail of the drug development process. Additionally, successful commercialization efforts

are predicated on demonstration of value during the course of clinical development, requiring different types of trials capable of evaluating changes in overall healthcare utilization following the introduction of innovative therapy; i.e., an effort which evaluates the impact of novel therapy on a 'system of care' in order to enable patient access. Given the unique technology represented by these products, educational programs for physicians and patients enhance informed adoption [99].

Table 12. Summary of research strategies for studying rare diseases and their advantages
Adapted from [102].

Strategy	Description	Expand access to studies and participants				Promote recruitment and retention	
		Minimize no. of required participants	Make use of conventionally underpowered studies	Maximize outcome information among participants	Facilitate confounding adjustment with sparse data	Maximize No of participants who receive treatment	Expand access to studies and participants
Study design options:							
Factorial designs	Two or more treatments can be simultaneously compared in a single group of study participants	X	-	-	-	-	-
Response-adaptive randomization	Increases participants' probability of being exposed to more effective treatment and reduces total sample size	X	-	-	-	-	-
Sequential designs	Can identify differences in treatments before the end of planned enrollment	X	-	-	-	-	-
Crossover, n-of-1, alternating designs	Using patients as their own controls both guarantees treatment and increases statistical efficiency	X	-	-	-	-	-
Use continuous outcome	As compared with binary outcome, continuous measures increase statistical efficiency	-	-	-	-	-	-
Use surrogate outcome	Can be measured before patients are lost to follow-up for hard clinical endpoints	-	-	X	-	-	-
Use composite outcome	Combining multiple outcomes into a single endpoint increases number of events	-	-	X	-	-	-
Use repeated measure outcome	Allowing patients to contribute more than one event can increase total number of events	-	-	X	-	-	-
Case-control sampling	Longer studies permit capture of more outcome events among participants	-	-	X	-	-	-
Case-control sampling	Reduces study size by sampling a portion of patients who do not experience an outcome	-	-	-	-	-	-

Strategy	Description	Expand access to studies and participants				Promote recruitment and retention	
		Minimize no. of required participants	Make use of conventionally underpowered studies	Maximize outcome information among participants	Facilitate confounding adjustment with sparse data	Maximize No of participants who receive treatment	Expand access to studies and participants
Recruitment and enrollment strategies:							
Focus on high risk patients	Outcomes are more likely to occur in high risk patients	-	-	X	-	-	-
Trial networks and distributed data networks	Infrastructure for multicenter studies can permit recruitment of larger and geographically diverse groups of patients	-	-	-	-	-	X
Statistical options:							
Increase α	Small patient populations may preclude sample sizes with sufficient power to detect effects using conventional thresholds	-	X	-	-	-	-
Propensity scores	Can permit adjustment for more potential confounders than outcome regression modeling	-	-	-	X	-	-
Incorporation into larger evidence context:							
Conduct study as part of prospectively planned meta-analysis	Individual small studies may not provide definitive evidence about a question, but can be combined to yield sufficient power	-	X	-	-	-	-
Incorporate study into bayesian framework	Small studies can help increase the certainty around a clinical question	-	X	-	-	-	-

Chapter 5 - General conclusions and future perspectives

In the last decades, legislation incorporating regulatory and economic incentives for orphan drug development has been introduced in several countries and regions worldwide. Comparing the Orphan Drug-based legislations, similarities exist in granting the designation in Europe, USA and Japan. However, there are differences in the key criteria used to determine whether a medicinal product can be considered an 'orphan drug'.

The EMA has been engaged in collaborations with the FDA's Office of Orphan Products Development since 2000 and with the MHLW and PMDA Orphan Drug Designation Service from Japan since 2010. Through collaborative efforts between these authorities and the assumption of parallel submissions procedure finally, aim to improve transparency of incentive programmes and provide early and frequent interactions between regulators and companies. It is hoped that a more global approach to the development of orphan medicines can be fostered.

At least 80% of rare diseases have genetic origins, thus the sequencing of the human genome and the analysis of critical proteins in the blood have profoundly impacted biopharmaceutical research and are yielding important new tools for understanding and treating a wide range of conditions. That is why medicines manufactured through biotechnology and gene technology can provide a solution to treat rare diseases. The rapid improvements in the area of biotechnology provide good expectations to develop more innovative medicines intended to treat rare diseases.

The number of orphan drugs approved each year is increasing. In 2015, about 47% of the novel drugs approved by FDA were approved to treat a rare or "orphan" diseases. Orphan drugs are highly innovative, especially compared to their non-orphan new molecular entities counterparts. Furthermore, a company that obtains orphan designation attracts interest from investors because of the clinical potential of the molecule being developed, the financial incentives accompanying the designation (grants, tax credits), and the regulatory support provided by the Authorities (e.g. Protocol Assistance). There are a few other factors that positively influence the economics of orphan drug development: timelines are typically shorter and more flexible pathway until marketing approval because of the lack of alternative treatments.

Repatha® (evoculumab) is a fully human monoclonal antibody (mAb) administered subcutaneously and developed by Amgen. FDA granted evolocumab an orphan drug designation for homozygous familial hypercholesterolemia (HoFH) a few years ago and last year this drug received marketing authorisation. Although, it is a recently approved drug, its innovative mechanism of action for the approved indications, positions Repatha in the top 20 sellers of orphan drugs projected to 2020 with sales of $2,695.29M for all indications (HoFH and HeFH). Repatha® was presented as a case study in this thesis.

Clinical trials involving therapies for rare diseases are challenging for various reasons, such as very or exceptionally low disease prevalence, small and heterogeneous patient populations, difficulty in recruiting and high attrition rates during R&D processes.
There are various strategies that sponsors can employ to plan for, and overcome, the clinical and regulatory challenges of orphan drug development. High levels of evidence come from well-designed and well-executed clinical trials. Improvements in patient recruitment, study design and study end-points, and closer collaboration with the Authorities and with patient´s associations are probably the key strategies that companies will assume to overcome clinical development challenges in orphan drug development in the future.

For the next few years the orphan drug market is expected to continue to grow. According to an EvaluatePharma report [19] and consulted Thomson Reuters Cortellis™ database, worldwide orphan drug sales will reach $178 Bn by 2020. Novel drugs such as Repatha, Darzalex, Uptravi and Tagrisso which were approved in 2015 are included in the Top 20, i.e. although recently approved their forecast places them in the Top 20 of orphan drug most profitable. Currently, this analysis validates the significance of developing new medicines for rare diseases in the global pharmaceutical market. This attention not only will potentially affect the lives of millions of individuals worldwide who suffer from rare diseases, but it will also propel the evolution of precision medicine.

Unfortunately, several widely recognized specialty drugs have made headlines in recent years, as their annual sales have skyrocketed into the billions, far beyond their original orphan market potential, thanks to added label orphan indications (as well as off-label use). On this way, sponsor could benefit from the regulatory and commercial incentives of orphan drug development. Currently, the Regulatory Authorities are planning measures to avoid this type of development.

References

1. *Orphan Drug & Rare Disease Development: Understanding the U.S. and European Regulatory Landscape*. Premier Research 2015 [accessced 2016 01 June]; Available from: https://premier-research.com/wp-content/uploads/2015/07/07-07-15_pr_orphandrugandraredisease_wp_v03.pdf.
2. ARNOLD, R., et al., *The role of globalization in drug development and access to orphan drugs: orphan drug legislation in the US/EU and in Latin America.* F1000Res, 2015. **4**: p. 57.
3. *What is a rare disease?* EURORDIS Rare Diseases Europe website [accessced 2016 16 April]; Available from: http://www.eurordis.org/content/what-rare-disease.
4. FIELD, M. and BOAT, T., *Rare diseases and orphan products*. 2010, Washington (DC): National Academies Press (US).
5. MOTTE, S., *Orphan Indications and Clinical Trials: Why Rare Diseases Warrant Special Treatment.* SynteractHCR, 2014.
6. *Communication From The Commission To The European Parliament, The Council, The European Economic And Social Committee And The Committee Of The Regions on Rare Diseases: Europe's challenges*, in *COM(2008) 679 final*. 2008, Commission of the European Communities: Brussels.
7. GONG, S., et al., *The availability and affordability of orphan drugs for rare diseases in China.* Orphanet Journal of Rare Diseases, 2016. **11**(1): p. 20.
8. CORNU, C., et al., *Experimental designs for small randomised clinical trials: an algorithm for choice.* Orphanet Journal of Rare Diseases, 2013. **8**(1): p. 1.
9. *Position on Rare Disease Research*. EURORDIS: Rare Diseases Europe website [accessced 2016 15 April]; Available from: http://www.eurordis.org/sites/default/files/EURORDIS_Rapport_Research_2012.pdf.
10. KONTOGHIORGHE, C., et al., *World health dilemmas: Orphan and rare diseases, orphan drugs and orphan patients.* World J Methodol, 2014. **4**(3): p. 163-88.
11. *Rare diseases: common issues in drug development guidance for industry. Draft Guidance*, in *FDA*. 2015.
12. KAKKIS, E., et al., *Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints.* Orphanet journal of rare diseases, 2015. **10**(1): p. 1.
13. *What is an orphan drug?* EURORDIS: Rare Diseases Europe website [accessced 2016 09 April]; Available from: http://www.eurordis.org/content/what-orphan-drug.
14. WINSTONE, J., et al., *Review and comparison of clinical evidence submitted to support European Medicines Agency market authorization of orphan-designated oncological treatments.* Orphanet journal of rare diseases, 2015. **10**(1): p. 139.
15. *Orphan Drugs*. Orphan Europe website [accessced 2016 17 February]; Available from: http://www.orphan-europe.com/about-us/orphan-drugs.
16. DUNKLE, M., *30-year retrospective: National Organization for Rare Disorders, the Orphan Drug Act, and the role of rare disease patient advocacy groups.* Orphan Drugs: Research & Reviews, 2014. **4**: p. 19-27.
17. MARIZ, S., et al., *Worldwide collaboration for orphan drug designation.* Nature Reviews Drug Discovery, 2016. **15**(6): p. 440-1.

18. O'CONNOR, D., *Orphan drug designation–Europe, the USA and Japan.* Expert Opinion on Orphan Drugs, 2013. **1**(4): p. 255-259.
19. EvaluatePharma®. *Orphan Drug Report 2015*. October 3rd:[Available from: http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD15.pdf.
20. KORCHAGINA, D., et al., *Orphan Designations and Approvals in the EU, USA and Japan*, in *ISPOR 18th Annual European Congress* 2015, Editor. 2015, Creativ Ceutical: Milan.
21. SAINT-RAYMOND, A. and LLINARES, J., *Orphan medicines: a success with a challenging future.* Expert Opinion on Orphan Drugs, 2013. **1**(3): p. 185-187.
22. LECOMTE, E., *Development of International Orphan Drug Policies*, in *ECRD*. 2014, Shire: Berlin.
23. MAVRIS, M. and CAM, Y., *Involvement of patient organisations in research and development of orphan drugs for rare diseases in Europe.* Molecular syndromology, 2012. **3**(5): p. 237-243.
24. DEASY, S., *5 things you need to know about international rare disease organisations*. 2013 DEBRA
25. *Rare Disease Day* Genzyme Rare Community website 2016 [accessced 2016 01 June]; Available from: http://genzymerarecommunity.com/rare-disease-day.
26. DOOMS, M., *Rare diseases and orphan drugs: 500 years ago.* Orphanet Journal of Rare Diseases, 2015. **10**(1): p. 1.
27. SALKELD, E., *The value of collaborative research in rare disease research*, in *Expert Opinion on Orphan Drugs*. 2016.
28. *Rare diseases* European Commission: Research & Innovation Health website [accessced 2016 10 April]; Available from: http://ec.europa.eu/research/health/index.cfm?pg=area&areaname=rare.
29. *Medicines for rare diseases*. European Medicines Agency website [accessced 2016 19 April]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp.
30. *Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products - State of Play 2015*. 2016 [accessced 2016 13 April]; Available from: http://ec.europa.eu/health/files/orphanmp/doc/orphan_inv_report_20160126.pdf.
31. *Report From The Commission To The European Parliament, The Council, The European Economic And Social Committee And The Committee Of The Regions: Implementation report on the Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final] and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)*, in *COM/2014/0548 final */*. 2014.
32. GAMMIE, T., LU, C., and BABAR, Z., *Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries.* PloS one, 2015. **10**(10).
33. *Webinar Review: Strategies for Rare Disease Studies and Orphan Drug Development in Europe*, in *Premier Research*. 2013.
34. *Orphan designation*. European Medicines Agency website [accessced 2016 15 May]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp.

35. *How to apply for orphan designation*. European Medicines Agency website [accessced 2016 08 May]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000519.jsp&mid=WC0b01ac05804ece5e.
36. *Procedure for orphan medicinal product designation* in *EMA/710915/2009 Rev. 13*. 2015, European Medicines Agency.
37. *Post-orphan medicinal product designation procedures*, in *EMA/62801/2015 Rev. 41*. 2016, European Medicines Agency.
38. *Orphan Medicines Figures 2000-2015*. European Medicines Agenciy 2016 [accessced 2016 29 April]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf.
39. *Orphan Medicines Regulation*. Eurordis: Rare Disease Regulation website [accessced 2016 29 April]; Available from: http://www.eurordis.org/content/promoting-orphan-drug-development.
40. *Scientific Advice Working Party*. European Medicines Agency website 2016 [accessced 2016 01 May]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000022.jsp.
41. EMA. *Annual Report 2015*. European Union 2016; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/05/WC500206482.pdf.
42. *Note for guidance on the format and content of the annual report on the state of development of an orphan medicinal product*, in *EMA/COMP/189/2001 Rev. 3b*. 2014, EMA.
43. MARIZ, S., et al., *The orphan framework as a new opportunity: an expert opinion.* Expert Opinion on Orphan Drugs, 2014. **2**(11): p. 1181-1186.
44. TARUSCIO, D., CAPOZZOLI, F., and FRANK, C., *Rare diseases and orphan drugs.* Annali dell'Istituto Superiore di Sanità, 2011. **47**(1): p. 83-93.
45. *Activities after orphan designation*. European Medicines Agency website [accessced 2016 18 May]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000554.jsp&mid=WC0b01ac058061ecbb.
46. *Marketing authorisation and market exclusivity*. European Medicines Agency website [accessced 2016 28 April]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000392.jsp&.
47. GUTIERREZ, L., et al., *Principles for consistent value assessment and sustainable funding of orphan drugs in Europe.* Orphanet journal of rare diseases, 2015. **10**(1): p. 1.
48. *List of Orphan Medicinal Products with Marketing Authorisation (as of May 2016)*. [accessced 2016 09 May]; Available from: http://www.eurordis.org/sites/default/files/omp-with-marketing-authorisation-may-2016.pdf.
49. *Register of designated Orphan Medicinal Products (by number)*. European Comission website [accessced 2016 01 May]; Available from: http://ec.europa.eu/health/documents/community-register/html/orphreg.htm#top.

50. RHEE, T., *Policymaking for Orphan Drugs and Its Challenges.* AMA journal of ethics, 2015. **17**(8): p. 776.
51. *Subpart C—Designation of an Orphan Drug*. Electronic Code of Federal Regulations. FDA 2016; Available from: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21.
52. FIELD, M. and BOAT, T., *Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs.* 2010.
53. JOHNSON, D., *Fast-tracking an orphan drug indication within a broader development project.* Expert Opinion on Orphan Drugs, 2014. **2**(2): p. 107-111.
54. *Designating an Orphan Product: Drugs and Biological Products*. U.S. Food and Drug Administration website [accessced 2016 18 May]; Available from: http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/default.htm.
55. *Developing Products for Rare Diseases & Conditions*. U.S. Food and Drug Administration website 2016 [accessced 2016 29 March]; Available from: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm.
56. *Orphan Drugs in the United States of America*. Orphanet website 2016 [accessced 2016 08 May]; Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=PT&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_USA.
57. *FDA at Rare Disease Day/ February 28, 2011*. U.S. Food and Drug Administration website 2015 [accessced 2016 21 April]; Available from: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm239698.htm.
58. FDA. *Novel New Drugs 2015*. 2016; Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM485053.pdf.
59. *Rare Pediatric Disease Priority Review Voucher Incentive Program*, in *Public Law 112-144-July 9, 2012*. 2012. p. 1094-1098.
60. ANTOS, J., *Common misconceptions about the orphan drug designation*, in *Pharmaceutical Commerce*. 2014.
61. *Subpart C–Designation of an Orphan Drug: 316.30 Annual reports of holder of orphan-drug designation*. Electronic Code of Federal Regulations. FDA 2015; Available from: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21.
62. REESE, J., *FDA Orphan Drug Designation 101*. 2014, Food and Drug Administration
63. *A Decade of Innovation in Rare Diseases 2005-2015*. EvaluatePharma 2015 [accessced 2016 16 May]; Available from: http://www.phrma.org/sites/default/files/pdf/PhRMA-Decade-of-Innovation-Rare-Diseases.pdf.
64. *Search Orphan Drug Designations and Approvals*. FDA [accessced 2016 17 May]; Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/.

65. *Interactions between the European Medicines Agency and U.S. Food and Drug Administration September 2009-September 2010* in *EMA/705027/2010* EMA, Editor. 2011.
66. RAO, G., et al., *Parallel Submissions for Orphan Designation with the FDA, EMA and MHLW/PMDA*. 2013, EMA.
67. MIZUSHIMA, H., et al., *International collaboration for a National Registry for Rare Diseases in Japan (Nambyo)*, in *Clinical Information Modeling Initiative (CIMI)*. 2014: Amsterdam.
68. SONG, P., W. TANG, and N. KOKUDO, *Rare diseases and orphan drugs in Japan: developing multiple strategies of regulation and research.* Expert Opinion on Orphan Drugs, 2013. **1**(9): p. 681-683.
69. *Overview of Orphan Drug/Medical Device Designation System*. Pharmaceutical Administration and Regulations in Japan 2009; Available from: http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html.
70. *Japanese Orphan Drug Designation* European Medicines Agency website 2013 [accessced 2016 02 March]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/10/WC500152531.pdf.
71. JAMBHEKAR, P., *Overview of Orphan Drugs in Japan.* Regulatory Focus, 2011: p. 14-18.
72. *Orphan Drugs in Japan*. Orphanet website 2016 [accessced 2016 28 February]; Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=PT&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_JAP.
73. *New Drugs Approved in May 2015 - FY 2015 (April - January)*. Pmda website 2015 [accessced 2016 29 May]; Available from: http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html.
74. *Orphan Drug database: Current as of the date May 25, 2015*. NIBIO 2016 [accessced 2016 25 May]; Available from: https://www.nibiohn.go.jp/shinko/orphan/english/pdf/h2705kisyoiyaku-hyo1_english.pdf.
75. *Registration opens for joint EMA/FDA/MHLW-PMDA orphan medicinal product workshop*. EMA 2013; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001997.jsp&mid=WC0b01ac058004d5c1.
76. *European Union - Japan orphan medicines cooperation*. EMA/488924/2012 2012; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/07/WC500130447.pdf.
77. HRONSZKY, I., *Expectations and visions in industrial practice. On the case of modern biopharmaceuticals.* Science, Technology & Innovation Studies, 2012. **8**(1): p. 37-60.
78. EvaluatePharma®. *World Preview 2015, Outlook to 2020*. 2015; 2015:[Available from: http://info.evaluategroup.com/rs/607-YGS-364/images/wp15.pdf.
79. HAYES, A., *The Biggest Biotech Companies.* Investopedia, 2015.
80. Gaze, L. and RODERICK, J., *The Economic Power of Orphan Drugs*, in *Thomson Reuters*. 2012.

81. *Why are biotech drugs relevant to orphan diseases?* . Europabio website [accessced 2016 13 May]; Available from: www.europabio.org/why-are-biotech-drugs-relevant-orphan-diseases.
82. PhRMA. *Rare Diseases: A Report on Orphan Drugs in the Pipeline*. 2013; Available from: http://phrma.org/sites/default/files/pdf/Rare_Diseases_2013.pdf.
83. *Frequently Asked Questions About Rare Diseases*. 2012 [accessced 2016 25 May]; Available from: https://www.genome.gov/27531963/faq-about-rare-diseases/.
84. *Rare Disease Programs*. Marina Biotech website 2016 [accessced 2016 25 May]; Available from: http://www.marinabio.com/pipeline/rare-disease-programs/.
85. ROOSWINKEL, R., MULDER, G., and DEVENTER, S., *Acquiring orphans.* Nat Biotechnol, 2014. **32**(3): p. 213-6.
86. MURAKAMI, M. and NARUKAWA, M., *Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan.* Drug Discov Today, 2016. **21**(4): p. 544-9.
87. *Creating a patientbased forecast*. 2010; Available from: http://ip-science.thomsonreuters.com/m/pdfs/TPP-Forecast-cwp-en.pdf.
88. Thomson Reuters, *Cortellis™* Competitive Intelligence database, 2012 [accessced 2016 15 July].
89. *Assessment Report: Repatha* EMA/CHMP/222019/2015 2015; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003766/WC500191400.pdf.
90. AMGEN, *REPATHA (evolocumab) injection, for subcutaneous use Initial U.S. Approval: 2015* A. Inc., Editor. 2015.
91. Physicians, N.G.f. *The Physician's Guide to Homozygous Familial Hypercholesterolemia (HoFH)*. 2014; Available from: http://nordphysicianguides.org/wp-content/uploads/2014/06/NORD_Physician%E2%80%99s-Guide-to-HOFH.pdf.
92. CUCHEL, M., et al., *Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society.* European heart journal, 2014. **35**(32): p. 2146-2157.
93. *Evolocumab: Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC).* FDA Briefing Document, 2015.
94. *The Science of Hope: the need, the challenges and three proven strategiesb for successful orphan drug development*. Premier Research 2014 [accessced 2016 20 june]; Available from: https://premier-research.com/wp-content/uploads/2014/12/The_Science_of_Hope_the_need_the_challanges_and_three_proven_strategies_for_successful_orphan_drug_development.pdf.
95. TAMBUYZER, E., *Rare diseases, orphan drugs and their regulation: questions and misconceptions.* Nature Reviews Drug Discovery, 2010. **9**(12): p. 921-929.
96. BELL, S. and SMITH, C., *A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials. gov.* Orphanet journal of rare diseases, 2014. **9**(1): p. 1.
97. O'CONNOR, D. and HEMMINGS, R., *Coping with small populations of patients in clinical trials.* Expert Opinion on Orphan Drugs, 2014. **2**(8): p. 765-768.

98. Secretariat, I.S., *Small Population Clinical Trials Challenges in the Field of Rare Diseases*. 2016.
99. MURPHY, M., *Rare Diseases: Meeting the Unique Challenges of Orphan Drug Development.* Applied Clinical Trials, 2016.
100. ALEMAYEHU, D., M. LEVENSTEIN, and. KNIRSCH, C *Statistical considerations for clinical trials in rare diseases.* Journal of Rare Disorders Vol, 2014. **2**(1): p. 18.
101. MULLARD, A., *FDA approves ultra-orphan drug on a 4-patient trial.* Nature Reviews Drug Discovery, 2015. **14**(10): p. 669-669.
102. Gagne, J., et al., *Innovative research methods for studying treatments for rare diseases: methodological review.* 2014.