



Flávia Patrícia Ribeiro Moreira

Orphan Drugs - A Regulatory, Ethical and Pharmacoeconomic Framework

**Dissertação do 2º Ciclo de Estudos Conducente ao Grau de Mestre em
Tecnologia Farmacêutica**

Trabalho realizado sob a orientação

do Professor Doutor Domingos de Carvalho Ferreira (Orientador) e do
Professor Doutor João José Martins Simões de Sousa (Coorientador)

Porto

Julho 2018

DECLARAÇÃO DE REPRODUÇÃO

É autorizada a reprodução integral desta dissertação apenas para efeitos de investigação, mediante declaração escrita do interessado, que a tal se compromete.

Agradecimentos

Em primeiro lugar, quero agradecer aos meus orientadores, Professor Domingos Ferreira e Professor João José Sousa, por toda a disponibilidade, apoio e sugestões de melhoria dadas ao meu trabalho.

Este trabalho é dedicado aos meus pais e ao meu irmão, por toda a paciência e por me acompanharem sempre na minha vida académica.

Um grande obrigado à minha família, em especial aos meus tios, madrinha, padrinho Luís e Tozé por toda a preocupação que sempre tiveram comigo e por me apoiarem nos meus momentos mais difíceis.

Obrigada por todo o apoio!

Acknowledgments

Firstly, I want to thank to my mentors, Professor Domingos Ferreira and Professor João José Sousa for all the availability, support and improvement suggestions given to my work.

This work is dedicated to my parents and to my brother, for all patience and for accompanying me always in my academic life.

A big thank to my family, in special to my uncles, godmother, godfather Luís and Tozé for all the worry that they always had with me and for supporting me in the most difficult moments.

Thank you for all support!

Resumo

É estimado que as doenças órfãs afetem mais de trezentos e cinquenta milhões de pessoas no mundo (1). Uma doença órfã é muitas vezes denominada como doença rara, mas estes termos são ligeiramente diferentes. Primeiramente, as doenças órfãs englobam doenças raras e Doenças Tropicais Negligenciadas. As doenças raras têm diferentes definições nos Estados Unidos de América e Europa, cada uma definida no referente regulamento sobre medicamentos órfãos, nomeadamente a Lei dos Medicamentos Órfãos e o Regulamento (EC) No. 141/2000. Acerca das Doenças Tropicais Negligenciadas, estas doenças afetam uma grande parte da população de países em desenvolvimento (conhecidos como países do terceiro mundo), e devido à baixa rentabilidade dos investimentos, a indústria farmacêutica não está aí focada.

Os dois regulamentos acima referidos foram desenvolvidos para o mesmo propósito: o desenvolvimento de novas terapias eficazes para combater doenças órfãs. Para isso, prevê-se muitos incentivos para os promotores, para serem aplicados antes, durante e após os processos de submissão de medicamentos órfãos, que serão discutidos neste trabalho. O Regulamento Europeu aplicável a medicamentos órfãos também incentiva os Estados Membro da Europa a terem as suas próprias metodologias para atingirem os mesmos objetivos globais. Acerca destas ações, será discutido como estão a ser aplicados e como é que os Estados Membros estão a gerir os seus incentivos, incluindo o exemplo de Portugal através dos números disponibilizados pelo INFARMED I.P.

A Organização Mundial de Saúde defende que um dos direitos de qualquer ser humano é o direito ao melhor padrão de saúde, mas um elevado número de doentes continua a sofrer com doenças que não têm um tratamento disponível e/ou efetivo. O desenho dos ensaios clínicos com medicamentos órfãos deve ser também muito bem estudados pelos promotores. Outros tipos de metodologias aplicáveis a este tipo de estudos são discutidos neste trabalho.

Uma discussão geral acerca das doenças órfãs será apresentada em relação aos três pilares fundamentais, a saber, abordagens regulatórias, éticas e farmacoeconómicas sobre o desenvolvimento de medicamentos órfãos.

Palavras-chave: doenças negligenciáveis; doenças raras; medicamentos órfãos; regulamento.

Abstract

It is estimated that orphan diseases affect more than three hundred and fifty millions of people around the world (1). An orphan disease is usually named as rare disease, but these terms are too little different. Firstly, orphan diseases comprise rare diseases and Neglected Tropical Diseases (NTDs). Rare diseases have different definitions in United State of America (USA) and Europe, each stated on the referred regulation regarding orphan drugs, namely the Orphan Drug Act and the Regulation (EC) No 141/2000. About NTDs, these diseases affect a large part of the population of countries in development (named as countries of the third world), and due to the poor rentability of the investments, pharmaceutical industry is not focused on it.

The two regulations referred above were developed for the same purpose: the development of new effective therapies to combat orphan diseases. For that, they foreseen many incentives for Sponsors, to be applicable pre, during and post submission processes of orphan drugs, which will be discussed in this work. The European Regulation applicable to orphan drugs also incentives Member States of Europe to have their proper methodologies to achieve the same global purpose. Along of these actions, it will be discussed how they are being applied and how Member States are managing their proper incentives, including the example of Portugal through numbers made available by INFARMED I.P.

The World Health Organization (WHO) defends that one of the right of any human is the right to the best standard of life, but a higher number of patients continue to suffer with diseases without an available and/or effective treatment. The design of the clinical studies with orphan drugs, should also be well studied by Sponsors. Other type of methodologies that can be applied for this type of the studies are discussed on this work.

An overall discussion about orphan diseases will be present, regarding the three fundamentals pillars, namely regulatory, ethical and pharmacoeconomic approaches on the development of orphan drugs.

Key words: negligence diseases; rare diseases; orphan drugs; regulation.

Table of Contents

1. Introduction	12
2. Orphan Diseases	13
2.1. Rare Diseases and NTDs.....	13
2.2. Epidemiology of Orphan Diseases	13
2.3. Causes of Orphan Diseases	15
2.4. Diagnoses and Treatment	17
2.5. Criteria on the Orphan Drugs Evaluation	17
3. Regulatory Framework for Orphan Drugs Submission.....	18
3.1. The Historical Context.....	19
3.2. The Orphan Drug Act	20
3.3. The Regulation (EC) No 141/2000	22
3.4. Other Incentives for Orphan Drugs Development	26
3.4.1 Workshops	26
3.4.2 Expert Groups on Rare Diseases	26
3.4.3 Programmes to Support Research on Rare Diseases	26
4. Ethical Considerations in Orphan Drugs Development	28
4.1. Ethical Standards applicable to the Clinical Research Conduct.....	28
4.2. Essential Principles and Scientific Evaluation of an Ethical Clinical Research Conduct.....	29
4.3. Duties and Rights of Clinical Study Participants	30
4.4. Informed Consent Form	31
4.4.1 The Informed Consent Process for Minors or Disabled Potential Participants .	33
4.5. Conflicts of Interest and Responsibility.....	34
4.6. The Use of Placebo in Clinical Studies.....	34
4.7. Conduction of Clinical Studies in Countries of the Third World	35
5. Clinical Studies with Orphan Drugs	36
5.1. Design of Clinical Studies.....	37
5.1.1 Single-Site and Multicentre Clinical Studies.....	37

5.1.2 Phases of Clinical Studies	38
5.1.3 Randomization at Clinical Studies	40
5.1.4 Clinical Studies Methodology.....	42
5.1.5 Clinical Studies Specific Design	42
5.1.6 Blinding in Clinical Studies	45
5.2. Standard Process of a Clinical Study	46
5.2.1 Since the Sponsor Contact until the Close-Out Visit	46
5.3. Natural History Studies.....	48
5.4. Clinical Studies Design for Orphan Drugs	50
5.5. Methodologies to Evaluate Clinical Studies	52
5.4.1 Jadad Scale	53
5.4.2 <i>António Vaz de Carneiro</i> Scale.....	54
5.4.3 Selection and Evaluation of Clinical Endpoints	55
6. Pharmacoeconomic Assessment in Orphan Drugs	56
6.1. Health Economic Assessment for Orphan Drugs.....	56
6.2. Specific Countries Incentives for Orphan Drugs Development	60
6.3. The Portuguese Example regarding Orphan Drugs Development	63
7. Conclusions	66
8. Bibliography	68
9. Annexes	79

Index of Figures

Figure 1 - Number of selected NTDs per country (based on 2009-2010 data and international borders). Adapted from Uniting to Combat Neglected Tropical Diseases burden map (22).....	14
Figure 2 - Application for orphan medicinal product designation to EMA, until 2017. Adapted from Orphan Medicines Figures, 2017 (47).	25
Figure 3 - Number of orphan medicinal products authorised in EU, until 2017. Adapted from Orphan medicines in the EU – leaving no patient behind, 2017 (48).	25
Figure 4 – Africa clinical studies distribution. Adapted from clinicaltrials.gov (67).	35
Figure 5 - Different phases of clinical studies (71). Understanding the Clinical Trial Process, 2016.	38
Figure 6 - Parallel design in a clinical study. European Patients' Academy, 2015 (76)....	43
Figure 7 - Cross-over design in a clinical study. European Patients' Academy, 2015 (76).	43
Figure 8 - Factorial design in a clinical study. European Patients' Academy, 2015 (76)..	44
Figure 9 - Matched Pair Trial design in a clinical study. European Patients' Academy, 2015 (76).....	45
Figure 10 - USA, Europe and Japan orphan designations per year (2003-2017). Evaluate Pharma, 2018 (90).	57
Figure 11 – Worldwide orphan sales compared with non-orphan drugs market. Evaluate Pharma, 2018 (91).	58
Figure 12 – Median cost per patient per year, based on the top one hundred drugs in the USA (2013-2017). Evaluate Pharma, 2018 (91).	58
Figure 13 – Evolution of the identification cards requests (2014-2017). Adapted from Direção Geral da Saúde, 2018 (94).....	63
Figure 14 – Investments done by Portugal on the treatment of rare diseases (2007-2017). Adapted from INFARMED,I.P., 2018 (95).	64
Figure 15 – Number of active substances used in Portugal for the treatment of rare disease (2007-2017). Adapted from INFARMED,I.P., 2018 (95).....	64
Figure 16 – Expenses with rare diseases by Portuguese public hospitals between January and April of 2018. Adapted from INFARMED,I.P., 2018 (96).....	65

Index of Tables

Table 1 - Summary of some NTDs epidemiology (number of people affected and countries). Adapted from Uniting to Combat Neglected Tropical Diseases, 2016 (18).	15
Table 2 - Causes and part(s) of the human body affected by preselected NTDs examples. Adapted from Uniting to Combat Neglected Tropical Diseases (18).	16
Table 3 – Items evaluated on the Jadad Scale. Adapted from Berger, et.al, 2010 (87). ..	53
Table 4 – Scale of António Vaz de Carneiro. Adapted from Carneiro, 2008 (86).....	54
Table 5 – Total of fee reductions processed in Europe. European Commission, 2015 (6).	62

List of Abbreviations and Symbols

CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CRF	Case Report Form
DALY	Disability-adjusted life years
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food & Drug Administration
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRDiRC	International Rare Diseases Research Consortium
MHLW	Japanese Ministry of Health, Labour and Welfare
NIH	National Institutes of Health
NTD	Neglected Tropical Diseases
PCT	Preventive Chemotherapy and Transmission Control
QALY	Quality-adjusted life-year
USA	United States of America
WHO	World Health Organization
WMA	World Medical Association

1. Introduction

According to National Institutes of Health (NIH), there are about seven thousand rare diseases around of the world, most of them with a genetic cause. In USA, twenty five-thirty millions of individuals live with one of rare disease, while in the European Union (EU) it is estimated that twenty seven-thirty six million suffer from them (2,3).

Until 1983, the year in which USA approved the Orphan Drug Act, the development of new drugs for orphan diseases was scarce and the process for their approval was slow (4). As the USA achieved promising results, other countries have adopted similar policies, such as Japan in 1993 and Australia in 1998 (5). In 2000 and with the same purpose, the EU enacted the Regulation [European Commission (EC)] No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

The above referred regulations comprise various incentives for the development and applications for submission of an orphan drug, such as protocol assistance, fee waivers, access to the centralised procedure, market exclusivity, workshops, etc. (6). Additionally in line with the Regulation (EC) No 141/2000, the European Medicines Agency (EMA) established a Committee for Orphan Medicinal Products (COMP), which is responsible for the analysis of orphan designations' applications (7). Stimulated by these news policies and by sales opportunity, the pharmaceutical industry is currently focused in the research and development for such diseases. As proof of this, more than 40% of new molecular entities were approved for orphan diseases between 2015 and 2016 and it is expected that the prescriptions of orphan drugs represents 21% of total drug prescriptions, excluding generics (8,9).

However, there are several barriers that orphan drugs must overcome since their research and development up to their introduction in the market. Since the population sample is limited and geographically dispersed, adequate clinical studies are only one of these barriers, which will be discussed afterwards.

Based on World Health Organization (WHO) principles, one of the fundamental rights of every human being is the access to the highest possible standards of health (10). So, it is essential that the government and society keep concerned about it, in order to patients needs be attended, independently of the number of patients affected.

2. Orphan Diseases

There is no a unique definition for orphan disease, but it has been used to designate a disease for which the development and market of drugs is considered to be commercially nonviable by pharmaceutical industries (11,12). Then, the term orphan disease can be divided into two different approaches - rare diseases or NTDs.

In this chapter, it will be present the profile of rare diseases and NTDs, including examples, epidemiology and causes for these conditions and actual diagnoses' methods and treatments.

2.1. Rare Diseases and NTDs

The rare disease's definition is based on its prevalence - number of people in a population who have a disease at a given time (13). According to the USA criteria described in Orphan Drug Act, a condition is defined as rare when affects less than two hundred thousand individuals. In EU, a disease or condition is considered rare when affects no more than five per ten thousand individuals, in accordance with Regulation (EC) No 141/2000. Further countries have other definitions for rare diseases, also based in the size of the population (e.g. Japan and Australia) (14).

NTDs are a group of infectious diseases that, according to the WHO estimate, affect one billion people of developing countries with tropical and subtropical environment (15). NTDs are also classified as orphan diseases, once they are more concentrated in the poorest and underprivileged countries that still not present incentives for development of treatments and their introduction in the market or, in most cases, the treatment is unavailable.

2.2. Epidemiology of Orphan Diseases

The epidemiology of rare diseases is imprecise, as their definition diverges according the prevalence established by each country. The rare diseases diagnosis process also demonstrates to be hard, due to the lack of medical knowledge and consequent absence of reports of this same disease, contributing to the prevalence's inaccuracy. Although affect adults, these conditions are more frequent in children, leading to their hospital stay about 40% more than adults (13).

Accessing the online platform Orphanet, it is possible to access a list with rare diseases ordered by its prevalence or incidence (the risk of developing a specific disease during a given period of time) (14). In the base of the list, the isolated frontonasal dysplasia appears with only one hundred cases described in literature (14,15). This condition is caused by a mutation in the family ALX gene and can be classified in three different types, according

with the specific gene affected (15). As this gene family is related with craniofacial development, more frequent symptoms are wide spaced eyes and broad nose (15).

According with the aforementioned platform, Somatostatinoma is an extremely rare disease with a lower incidence: one case per forty million. This condition is a neuroendocrine tumour located in pancreas or gastrointestinal tract, caused by an abnormal secretion of somatostatin hormone in adults (16). Other examples of rare diseases will be timely discussed.

Regarding NTDs, they are more prevalent in children of the Third World countries, namely in Sub-Saharan Africa (17). In the document “WHO’s Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases: A Roadmap for Implementation”, more known as “WHO Roadmap”, seventeen NTDs were previously selected according with their probability of control and elimination, being defined strategies and goals to be reached up to 2020 regarding this conditions (17,18). Pharmaceutical companies and international community – including donor representatives, country representatives, foundations and non-governmental organizations - prepared some meetings in order to support these WHO goals and, on 30 January 2012 were selected ten NTDs of those who were previously selected by WHO as diseases for immediate assistance (17,18). The distribution of these NTDs (Trachoma, Chagas disease, Dracunculiasis, human African trypanosomiasis, Lymphatic filariasis, leishmaniasis) is shown on the figure 1:

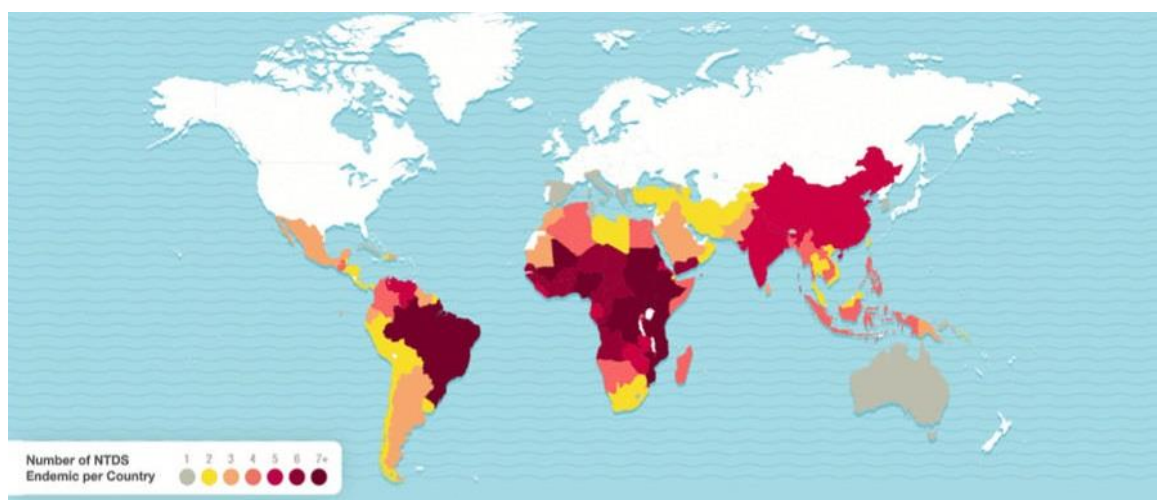


Figure 1 - Number of selected NTDs per country (based on 2009-2010 data and international borders). Adapted from Uniting to Combat Neglected Tropical Diseases burden map (22).

Furthermore, the table 1 summarizes the number of people affected by these ten NTDs and their geographical localization, in accordance to Uniting to Combat Neglected Tropical Diseases available data:

Table 1 - Summary of some NTDs epidemiology (number of people affected and countries). Adapted from Uniting to Combat Neglected Tropical Diseases, 2016 (18).

NTD	NUMBER OF PEOPLE AFFECTED	AFFECTED COUNTRIES
Trachoma	192 million	42 countries in America, Africa, Asa, Australia and Middle East
Chagas disease	6 million	21 countries in Latin America
Dracunculiasis (Guinea worm disease)	25	4 countries in Africa
Human African trypanosomiasis	2 000	Africa
Lymphatic filariasis	67 million	62 countries in Latin America, Africa and Asia
Leprosy	175 000	Brazil, India and Indonesia
Onchocerciasis	26 million	Latin America and sub-Saharan Africa
Soil-transmitted helminths	1,5 billion	America, sub-Saharan Africa, China and South-East Asia
Schistosomiasis	218,2 million	78 countries in Latin America, Africa and Asia
Visceral leishmaniasis	21 646	Latin America, Africa and Asia

Analysing the table 1, it can be concluded that Dracunculiasis, Human African trypanosomiasis, Leprosy and Visceral leishmaniasis are being progressively eradicated, but the same does not apply for remaining diseases presented. Regarding geographical distribution, the African is more affected by NTDs, followed by Latin America. So, there is still a long way to achieve WHO goals for 2020, given that lot of people are at risk.

2.3. Causes of Orphan Diseases

In most cases, a rare disease is caused by genetic aspects, that can be transmitted between generations of the same family (the condition is hereditary) or, by other side, can occur isolated in a single individual, emerging frequently as rare cancers, infections or diseases of the immune system (2).

Although the knowledge of rare diseases causes is frequent in most of cases, the mechanism, diagnose or/and treatment can be totally or partially unknown (19).

As NTDs are more prevalent in countries without conditions of sanitation, potable water, and with healthcare lacks, these conditions are frequently caused by bacterial infections or by parasites (20). The table 2 summarizes causes and part(s) of the human body affected, regarding the preselected NTDs by WHO to control or eliminate up to 2020:

Table 2 - Causes and part(s) of the human body affected by preselected NTDs examples. Adapted from Uniting to Combat Neglected Tropical Diseases (18).

NTD	CAUSE	PART OF THE HUMAN BODY AFFECTED
Trachoma	Bacteria	Eyes
Chagas disease	Parasites	Heart, colon and oesophagus
Dracunculiasis (Guinea worm disease)	Parasites	Skin
Human African trypanosomiasis	Parasites	Central nervous system and brain
Lymphatic filariasis	Parasites (mosquito-transmitted disease)	Lymph system
Leprosy	Bacteria	Skin, nerves and muscles
Onchocerciasis	Parasites	Skin, eyes and other organs
Soil-transmitted helminths	Parasites	Not affect a specific part of the human body, but causes malnutrition and anaemia
Schistosomiasis	Parasites	Skin, urinary system and intestinal system
Visceral leishmaniasis	Parasites	Immune system, bone marrow and internal organs

As it is possible to see in the previous table, these NTDs affect various parts of the body, being that they can progress to the rest of body and be fatal.

2.4. Diagnoses and Treatment

Many conditions began to be possible to diagnose since the Human Genome Project, an international scientific research completed in 2003 by NIH and the U.S. Department of Energy, which was performed to sequence the human genome and for genes mapping and identification (21). Regarding rare diseases, physicians have little contact in their clinical practices, which difficult their diagnoses process.

Furthermore, the treatment is unknown for most of rare diseases once their mechanism of action is poorly understood yet. In order to advance in research and in the development of treatments for these conditions, many patients who suffer from rare diseases, together with their families had created organizations. An example of this is FACES – The National Craniofacial Association, an organization that provides support to USA population with craniofacial differences, including for example, people who suffer from isolated frontonasal dysplasia (13,22). Additionally, as will be discussed in the chapter 3, the creation of the Orphan Drug Act along with incentives, fee reductions, market exclusivity and funds were essential for the increase of the research, which improved the knowledge of pathophysiology and that consequently, led to the development of new drugs for rare diseases' treatment.

Regarding NTDs, while the treatment has progressed for most of them, the same is not true for their diagnosis process. Although the existence of sensitive and specific diagnostic methods for most infectious diseases, they are commercially unviable in developing countries, compromising the treatment of NTDs (23). Relatively to their diagnosis and treatment, NTDs can be divided in to main groups: for the first group, the diagnosis process is well established, and patients can resort to mass drug administration; for the second group, the diagnosis is more difficult and costly, which comprise the treatment availability. The preventive chemotherapy is the main tool and it is implemented the Preventive Chemotherapy and Transmission Control (PCT), that consists in providing technical guidelines and tools to improve the coordination and cost-effectiveness of NTDs eradication or control programs (24).

Furthermore, there is also the surgery possibility for some NTDs (e.g., for trachoma), but it is crucial to take measures to provide safe water, hygiene and sanitation for this population, in order to eliminate transmission or to achieve lower prevalence of NTDs (25).

2.5. Criteria on the Orphan Drugs Evaluation

Related with the submission of a marketing authorisation application of medicinal products, including orphans, Sponsors are advised by competent authorities to check if there are other medicinal products under market exclusivity protection (26). Regarding

orphan designation, if another orphan medicinal product is registered for the same therapeutic indication as the Sponsor is proposing for his orphan medicinal product, the application form may indicate this on the appropriate section (26). Market exclusivity in EU of a designated orphan medicinal product is in force during a period of ten years, which means that any other application for a marketing authorisation is not accepted during this period for the same therapeutic indication if the product is considered a similar medicinal product (26,27). According to Article 3 of Regulation (EC) No 847/2000, a similar medicinal product is

“a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication” (28).

Regarding the definition of a similar active substance it includes:

“an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism” (28).

Identical active substances include isomers (or a mixture of them), complexes, esters, salts, non-covalent derivatives or structural analogues (minor changes in the molecular structure comparing with the original active substance) (28). The definition about an identical active substance comprises also the same macromolecule or one with changes in its molecular structure (proteinaceous, polysaccharide and polynucleotide structures or closely complex partly definable substances) and a medicinal product with the same radiopharmaceutical active substance or one with a different radionuclide, ligand, site of labelling or other that acts via the same mechanism (28). About the mechanism of action, orphan medicinal products should be considered similar when their active substances bind the same pharmacological target (receptor, enzyme, channel, carrier or intracellular coupling process) and have the same pharmacodynamic effect (action of the active substance on the body) (29).

3. Regulatory Framework for Orphan Drugs Submission

The legal background in force for orphan designation and submission process is provided by EMA or by U.S. Food & Drug Administration (FDA), as applicable. In this chapter it will be discussed the legal progress and principal fundamentals of legislation related with orphan medicinal products, especially the Regulation (EC) No 141/2000, the Regulation No 847/2000 and the Orphan Drug Act.

3.1. The Historical Context

Although incessant progress in medicine, the lack of knowledge for several diseases that currently affect few people around the world continued to keep the society worried about it. In 4 January 1983, the USA introduced the Orphan Drug Act, a compilation of recommendations with the main objective to improve the development of new diagnosis and treatments for orphan diseases (30). The Orphan Drug Act presents incentives for the research and development of orphan drugs, such as exemption of the application fee for FDA approval and a marketing exclusivity period of seven years for these products. In 1984 it was issued an amendment of the Orphan Drug Act, since it was necessary to clarify the definition of a rare disease to facilitate the FDA working (4). In 29 December 1992, FDA issued the Orphan Drug Regulation that consists in the implementation of the Orphan Drug Act (30,31). In 12 June 2013, an amendment to Orphan Drug Regulation became effective in order to clarify and to improve the orphan designation process (30,32).

As the Orphan Drug Act results were demonstrating the importance of existence of a policy that defines the orphan diseases concept and that provides crucial benefits for its research and development, the EU followed the USA example: considering this area as a priority, in 1998 the EU adopted a Proposal for a European Parliament and Council Regulation on Orphan Medicinal Products (33). After a revision process, the European parliament accepted the final version of the Regulation (EC) No 141/2000 - or Regulation on Orphan Medicinal Products – and in 24 January 2000 it entered into force (33). With focus on research and development of new treatments for orphan diseases, this Regulation provides protocol assistance, direct access to the Community centralised procedure and offers a market exclusivity period of ten years (33). Inherent to this regulation, the EC selected the members to be part of the COMP, a committee designated to cooperate in the decisions about the designations of medicinal products as orphans (33). The constitution of this committee is established by the Regulation (EC) No 141/2000, being discussed in the next subchapter.

At the same year, the EC published the Regulation (EC) No 847/2000 with the main purpose to establish the necessary evidences that concerned medicinal product meets criteria to be designated as an orphan medicinal product (28,34).

In order to help sponsors in the compilation of documents needed for the application of an orphan medicinal product designation, EC published in 2002 the “Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another” (33).

On 12 December 2016, it was published by the European Parliament the Regulation (EC) No 1901/2006 about medicinal products for paediatric use. Related with orphan medicinal

products, this Regulation determines that the marketing exclusivity period of ten years can be prolonged to twelve years, if studies carried out with these medicinal products are in compliance with a pre-established paediatric investigation plan (34,35).

In 2008, EC published the “Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000”, a guideline that explains the application of six years for the period of the market exclusivity, instead of ten years, which will be clarified with more detail in a next subchapter (33). In the same year, the EC published the “Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000”, a guideline issued to clarify the procedure to follow in the assessment of the similarity between medicinal products and orphan medicinal products that are benefiting of the market exclusivity period (33). To provide a guide document related with the application of the Article 3, 5 and 7 of the Regulation (EC) No 141/2000 in the orphan designation process, the EC publish two years ago a Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) N° 141/2000 on orphan medicinal products (33).

The following subchapters will summarise principal points established in the Orphan Drug Act and in the Regulation (EC) No 141/2000.

3.2. The Orphan Drug Act

The FDA is the regulatory body in the USA responsible for ensuring the protection of public health, for regulating the manufacture, marketing and distribution of the following products and to guarantee that the following products are safe and have the appropriate quality and efficacy to be used:

- Food, including dietary supplements, bottled water, food additives, infant formulas and other food products;
- Human drug;
- Biological products, including vaccines, blood and blood products, cellular and gene therapy products, tissue and tissue products, allergenics;
- Medical devices, including simple and complex technologies, dental devices, surgical implants and prosthetics;
- Cosmetics;
- Veterinary products, including food and veterinary drugs and devices;
- Microwaves and x-ray equipment.

FDA also regulates manufacturing, marketing and distribution of tobacco products, being concerned in the reduction of its consumption.

FDA is the entity responsible to put in action the Orphan Drug Act. Regarding this public law, its main purpose is to improve the research and development of drugs intended for the

treatment of rare diseases, providing many incentives for Sponsors interested in submitting orphan drugs applications.

Before Orphan Drug Act be written, there was no consensual definition for orphan drugs: some experts defended that it would be drugs for the treatment of rare diseases and others advocated that it should be drugs developed for countries of the Third World (4). So, Orphan Drug Act authors decided that this legislation should be addressed to the research and development of drugs for rare diseases, defining the term “rare disease or condition” as:

“any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug” (36).

With this definition, FDA had some difficulties to evaluate if the submitted applications fell into the above definition and so in 1984, it was issued an amendment to the Orphan Drug Act clarifying it, based on the prevalence and commercial viability criteria, redefining “rare disease or condition” as any disease or condition that:

“affects less than 200,000 persons in the United States”

or,

“affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug” (37).

In order to reach its main purpose, the Orphan Drug Act established the creation of a group named as Orphan Products Board, constituted by the following members:

- Assistant Secretary for Health of the Department of Health and Human Services;
- FDA representatives;
- NIH representatives;
- Centers for Disease Control;
- Other members delegated by the Secretary (36).

In protocol development phase there is an incentive fixed by Orphan Drug Act regarding the possibility given for Sponsor to design open protocols for clinical studies, allowing the inclusion of patients with the rare disease to which the drug is being designated (36). Other incentive that Orphan Drug Act foreseen is the return to the Sponsor of half the costs invested in the clinical research of a medicinal product that was designated as an orphan medicinal product (38).

In title 21 (Food and Drugs) of the Electronic Code of Federal Regulations published by USA government, the part 316 is concerned in orphan drugs and provides information about what the content and format that a request for orphan-drug designation should have (39).

The relevant part of this Electronic Code of Federal Regulations is provided for consultation in Annex I. After being submitted, FDA is responsible to verify if orphan designation criteria are met. If FDA concludes that information provided is insufficient, incomplete or it has errors, a deficiency letter will be sent to the concerned Sponsor (39). After issuance of the deficiency letter, the Sponsor must answer to FDA within a period of one year (39).

If orphan drug designation is accepted by FDA, the Orphan Drug Act can grant a market exclusivity period of seven years for these medicinal products, which constitutes an incentive for the research and development of such drugs, since it is provided more two years when compared with drugs with a new chemical entity (40). Currently, around six hundred and ninety orphan drugs received a marketing approval by FDA since Orphan Drug Act publish (41).

3.3. The Regulation (EC) No 141/2000

In Europe, EMA is the pharmaceutical competent authority responsible to evaluate the scientific suitability and to follow-up the security of medicinal products that circulate or will be circulating in EU pharmaceutical market. For marketing authorizations of orphan drugs, the Sponsors must to request them to EMA, by a centralized procedure, which allows a marketing authorisation at the same time in all Member States. This centralized procedure must be followed in the next cases:

- Biotechnology medicines;
- Human medicines that contain a new active substance to treat conditions as acquired immune deficiency syndrome, cancer, diabetes, neurogenerative diseases, immune dysfunctions or viral diseases;
- Advanced-therapy medicines (e.g., tissue-engineered medicines);
- Veterinary medicines used for growth and yield improvement (42).

Regarding orphan drugs, the Regulation (EC) No 141/2000 was published in the Official Journal of the European Communities on 22 January 2000 with the purpose to establish:

“...a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products” (27).

The Regulation (EC) No 141/2000 lays down the criteria for a medicinal product be designated as an orphan medicinal product, but more detailed information about the necessary proofs of criteria achievement are established in Regulation (EC) No 847/2000. The first criterion is the inexistence of a method for diagnosis, prevention or treatment for the condition or, the medicinal product proposed for the designation should present substantial advantages when compared with the available method. To beyond these, the

proposed medicinal product should follow one of the next criteria to be designated as an orphan medicinal product:

- Prevalence criteria – the medicinal product that is being designated as an orphan medicinal product is proposed for the diagnostic, prevention or treatment of a condition that affects less than five in ten thousand people, or
- Neglected diseases – when is not foreseen the return of the investments needed for the research and development of the medicinal product that is being designated as an orphan medicinal product, being necessary incentives for its arrival to the market in order to diagnostic, to prevent or to treat certain condition.

As discussed in the subchapter 3.1, the Regulation (EC) No 141/2000 forecasts the constitution of a COMP to evaluate the requests for orphan medicinal product designations. COMP members are designated for a period of three years and its constitution is the following:

“one member nominated by each Member State, three members nominated by the Commission to represent patient’s organisations and three members nominated by the Commission on the basis of a recommendation from the Agency” (27).

Prior the submission of an application for an orphan medicinal product designation, it is established in the Regulation (EC) No 141/2000 that EMA should provide protocol assistance when Sponsors request it. Since the referred Regulation was published until 2015 (last data available from EC), EMA carried out nine hundred and fifty one protocol assistance procedures, which include regulatory assistance and scientific advice on non-clinical and clinical development in order to provide high-quality, effective and acceptably safe orphan medicinal products for concerned patients (6). The documents needed for the submission of the application are established in the Guidance for sponsors provided by EMA – “Procedure for orphan medicinal product designation”, and are attached as an excerpt of it in Annex II (43). Then, this application will be assessed by COMP after being validated, which is responsible to provide an opinion within ninety days. If it is necessary more information about the application, the Sponsor should submit it within a period of ninety days after reception of the COMP opinion. When the COMP final opinion is formed, the EC notifies the Sponsor with the final decision within thirty days and EMA and other competent authorities receive also this final decision. In case of a favourable decision, the concerned medicinal product is added to the Community Register of Orphan Medicinal Products (43). However, a marketing authorisation was not reached yet: after acceptance of an orphan medicinal product designation, the Committee for Medicinal Products for Human Use (CHMP) evaluates them, according with the quality, safety and efficacy of the concerned medicinal product (44).

The EC provides to EMA a percentage of the EU budget for the reduction of fees associated with all procedure, namely fees related with protocol assistance, applications for marketing authorisation, inspections and renewals (6).

The referred Regulation also forecasts situations in which an orphan medicinal product can be withdrawn of the Community Register of Orphan Medicinal Product when:

- Sponsor requests it;
- Orphan designation criteria are no longer met before its market authorisation;
- The market exclusivity period ends (27).

As referred above, the Regulation (EC) No 141/2000 lays down in article 8 that when an orphan medicinal product receives a marketing authorisation in EU, it cannot be accepted other application during a period of ten years for the same therapeutic indication if the product is considered a similar medicinal product (27). However, this period can be decreased to six years if the orphan designation criteria are no longer met (27). Related with the submission of an application of a medicinal product similar to an orphan medicinal product under the period of market exclusivity, it can be accepted if:

- The first applicant gave his authorisation for it, or
- The first applicant is unable to provide the necessary quantities of the orphan medicinal product, or
- The second medicinal product is clinically superior, although similar to the original orphan medicinal product (27).

Beyond protocol assistance, fee waivers, access to the centralized procedure, and market exclusivity period, Community and Member States should provide other incentives for the improvement of the research and development of orphan medicinal products, which must be detailed in an updated inventory published by EC (27,45). This topic will be discussed in more detail in the next subchapter.

Until 2017, from a total of 2 974 received applications for orphan medicinal products designations, COMP approved about 66% of them, as it is showed on the figure 2:

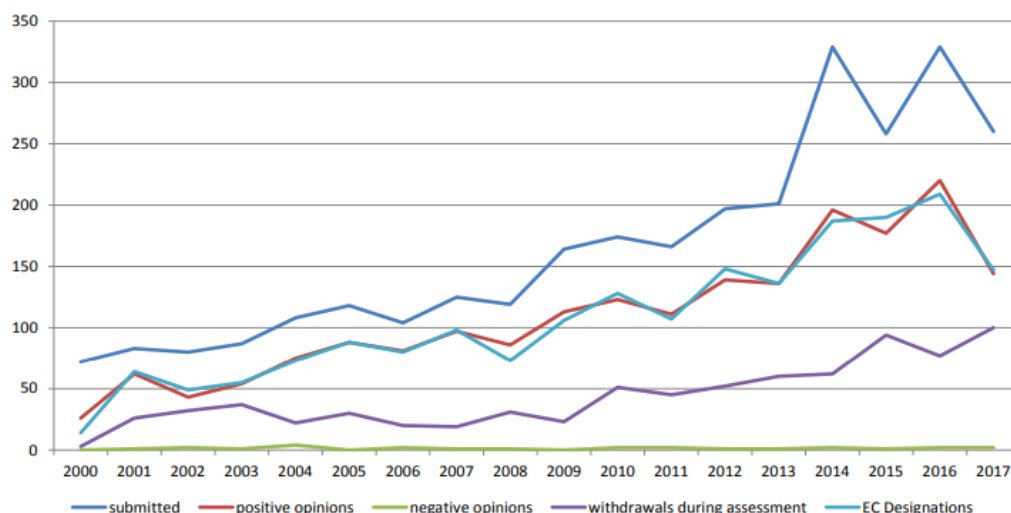


Figure 2 - Application for orphan medicinal product designation to EMA, until 2017. Adapted from Orphan Medicines Figures, 2017 (47).

Relatively to the distribution of the above referred applications for orphan medicinal products, most of them (about 34%) were antineoplastic agents and 55% were requested for orphan diseases that affect both paediatric and adult population (46). Until 2017, from the total orphan designations requests, one hundred and forty-two orphan medicinal products received a marketing authorisation in Europe, as shown in the figure 3:

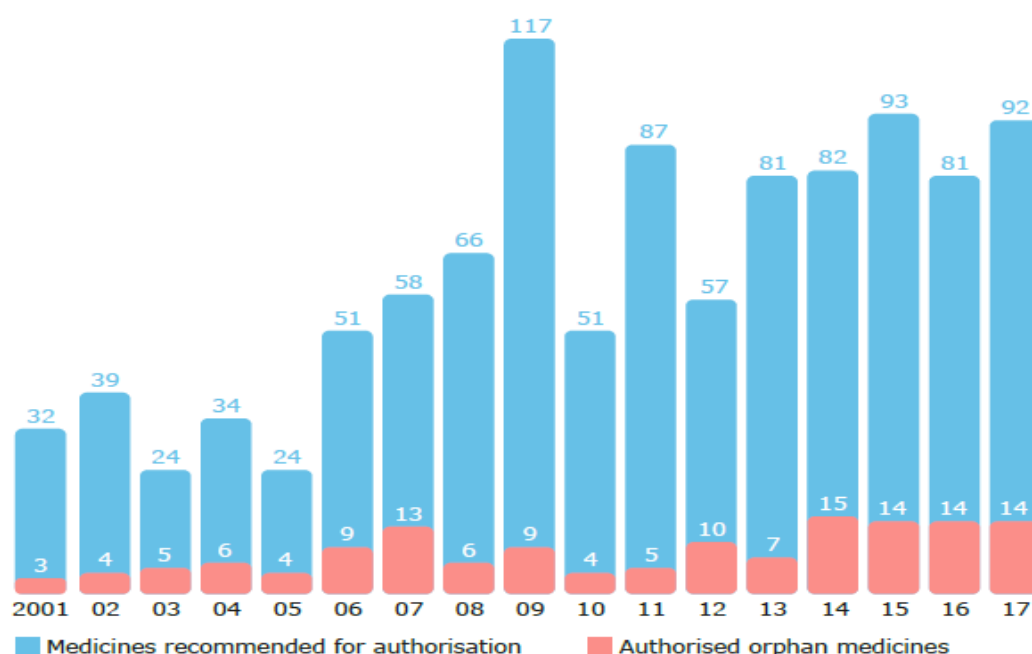


Figure 3 - Number of orphan medicinal products authorised in EU, until 2017. Adapted from Orphan medicines in the EU – leaving no patient behind, 2017 (48).

A practical example of an orphan designation process submitted to EMA is given in Annex III for consultation. In this example, it is presented a summary of the process for orphan designation of alpha-galactosidase A for Fabry disease treatment.

3.4. Other Incentives for Orphan Drugs Development

As it was mentioned on the above subchapters, the legislation regarding orphan drugs development provides many financial incentives for it, in order to make them available for affected patients. Furthermore, other incentives are being implemented by competent authorities as it will be discussed in this subchapter.

3.4.1 Workshops

Until 2015, EMA organized eleven workshops with Sponsors, to clarify doubts related with orphan drugs designation process (6). Worldwide workshops are also organized, for example the workshop that was realized in 10 March 2014 by EMA, that joined FDA, Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (the Japanese regulatory agency that works together with MHLW) (47). This workshop had the purpose to provide more information about the procedures on orphan medicinal products designation followed up by above competent authorities and to show programmes that are available to promote the development of these medicinal products (47).

3.4.2 Expert Groups on Rare Diseases

On 30 November 2009, the EC published a decision to establish a Committee of Experts on Rare Diseases, which has been replaced by the EC Expert Group on Rare Diseases in accordance with the Commission Decision of 30 July 2013 (6). This group should provide support to EC on orphan drugs development and has the following responsibilities:

- To contribute for guidelines and recommendations' writing;
- To provide recommendations and implementing EU activities related with rare diseases.

3.4.3 Programmes to Support Research on Rare Diseases

Beyond exclusivity period and tax credits, the Orphan Drug Act predicts the creation of incentive programs, such as the **Orphan Products Grant Program**, a set of funds to support clinical investigations on new potential therapies for rare diseases (38). Currently,

this program offers about fourteen million dollars to support one hundred of clinical investigations per year (38).

In Europe, some framework programmes were issued to support financially the research on rare diseases for the development of orphan medicinal products. An example of such programmes is the **Seventh Framework Programme for Innovation and Technological Development**, which started in 2007 and it was active until 2013, and that make available over six hundred and twenty million euros for one hundred and twenty projects focused into research of rare diseases and into preclinical and clinical development of orphan drugs (6).

Currently, **Horizon 2020** is the biggest programme in EU focused on research and innovation of several areas, with about eighty billion euros of funds for the investment and being available until 2020 (48). Regarding rare diseases, two projects are integrated in Work Programme 2016-2017 of Horizon 2020, namely SC1-PM-03-2017 and SC1-PM-08-2017, which are focused on the research of new diagnostic techniques and therapies for rare diseases (49).

Due to the diversity of rare diseases, the research community is dispersed by several countries, which can cause delays on development of new orphan medicinal products (50). In order to resolve this issue, the EC established in 2011 the **International Rare Diseases Research Consortium** (IRDiRC), a global consortium constituted by funders and patients organizations, with the main purposes to increment the delivery of two hundred new orphan drugs up to 2020 and to develop diagnostic methods for these rare diseases for which the orphan drugs were developed (6,51). As these purposes were reached in the begin of 2017, IRDiRC established new goals to be achieved until 2027:

- The diagnosis of rare diseases known by the medical community will be made available within one year;
- All patients with unknown conditions will be signalized in a global network to be investigated;
- One thousand new orphan medicinal drugs will be available to treat rare conditions;
- It will be developed evaluations of the diagnosis methods' accuracy and of the treatment efficacy of patients with rare diseases (52).

As a global consortium, the IRDiRC has selected a set of key resources (e.g. online platforms, guidelines, standards, etc.) to improve the search process about rare diseases (53). One of these recognized resources is Orphanet, referred in the subchapter 2.2 as an online platform supported by EC funds and that was established in 1997 (54). The Orphanet platform offers a common terminology, the ORPHA numbers, which are fundamental for

mutual recognition and understanding of each rare disease all over the world, contributing for a faster research and development of medicines for their diagnostic and treatment (54).

Relatively to devices, other programs were created to improve the development of newly safe and advantageous devices targeted for the treatment of rare conditions, namely the **Humanitarian Use Device** and **Humanitarian Device Exemption** (38).

4. Ethical Considerations in Orphan Drugs Development

On 10 December 1948, the United Nations General Assembly published an historical and fundamental document to protect the human rights, named as the Universal Declaration of Human Rights (55). The article 3 of the Universal Declaration of Human Rights sustains the right to life by everyone, that remits indirectly to the right to health (55). Making part of WHO principles, there is also the right by everyone to the “highest attainable standard of health” (10). In 2006, this right was also adopted by the United Nations on the Convention on the Rights of Persons with Disabilities, which concerns the orphan diseases, since they cause always disabilities in patients who suffer from that.

However, patients who suffer from orphan diseases not always have access to the best health care standards. Despite all advances in orphan drugs development, many hurdles remain on diagnosis and treatments of them: most of rare diseases still without an available diagnosis technique and/or an available treatment and thousands of people who suffer from NTDs still die every day.

In a survey conducted in Europe and directed to orphan diseases patients, it was concluded that 41% of them were incorrectly diagnosed at least one time before receiving the correct diagnosis (56). Due to lack of knowledge about rare diseases by medicine and large geographical distribution of the few patients who suffer from them, there are many difficulties in planning and in the conduction of clinical studies with orphan drugs, resulting in frequent delays or in the inexistence of new orphan drugs. Beyond these ethical approaches discussed above, other ethical general concerns related with the clinical studies realisation are also applicable clinical development phase for in orphan drugs, which will be discussed in this chapter.

4.1. Ethical Standards applicable to the Clinical Research Conduct

In response to the terrible experiences with humans practiced during the World War II by physicians and Nazi investigators, in 1947 it was published the **Nuremberg Code**, the first document focused on ethical questions in clinical research conduct. The Nuremberg Code came to highlight that is essential the voluntariness of the informed consent and emphasize the rights of participants, always considering their maximum protection (57). This historical

document also establishes that it is fundamental the existence of previous scientific evidences before to advance with any clinical research, predicting the achievement of benefits for society and taken always into account an analysis of benefits and risks foreseen to participants (57).

After one year of the Nuremberg Code publication, it was issued the **Universal Declaration of Human Rights** as mentioned above, that also came to underline the rights of clinical research participants.

However, many experiences were realized in vulnerable communities between 1960 and 1970, such as in ethnic minorities or institutionalized people so, it was concluded that the Nuremberg Code principles were not having the desired impact in the medical community. Furthermore, during the decade of 60, ten thousand women were included in a clinical study with Thalidomide without knowing that they were participating in such study. Many of these women were in fertile age, which results in the birth of about ten thousand newborns with phocomelia, a congenital condition that prevents the normal development of the lower and upper limbs (58). In order to establish ethical principles and specific guidelines for medical research involving human subjects, the World Medical Association (WMA) developed and issued in 1964 the **Declaration of Helsinki** (59). Along these years, the WMA organized general assemblies all over the world, which has been result in new amendments of the Declaration of Helsinki. This declaration is to be firstly adopted by physicians, but also by the remaining personnel involved in clinical research activities (59). The Declaration of Helsinki establishes that the well-being and rights of participants must be always defended by the physician, taking precedence over any new knowledge gained from clinical research (59). This declaration also refers the additional protection given to groups and individuals considered as vulnerable, and includes the acceptable circumstances to use a placebo, a subject that will be treated in a next subchapter due to its associated ethical controversies (59).

In 18 April 1979, it was issued the **Belmont Report** by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report presents the ethical principles considered as essential for the conduct of the clinical research, such as: the principle of respect, the principle of beneficence and the principle of justice (60).

4.2. Essential Principles and Scientific Evaluation of an Ethical Clinical Research Conduct

The planning of any clinical study makes part of a scientific method: there are an observation previously to a question. This question will be a basis to articulate a hypothesis

to be tested in the clinical study (e.g. if a test medicine has a better relation between benefits and risks than the reference medicine, etc.), which will determinate the study design and all related parameters (e.g. inclusion and exclusion criteria, etc.). The clinical study should have the purpose to solve a relevant problem for the society but taken into account that the potential benefits are higher than risks. This balancing is related with the beneficence principle, one of the ethical principles applicable for a clinical study conduct, as will be discussed below.

Any human action should be conducted in accordance with ethical principles. Regarding the clinical research, there are some ethical principles applicable for its conduction that can be highlighted, such as:

- The autonomy principle, respecting all participants but with special attention of those who have their autonomy diminished or when they are vulnerable population;
- The beneficence principle, which requires that actions promote the maximum well-being of patients, meaning that the expected benefits always outweigh the risks;
- The justice principle, which requires equity in the distribution of risks and benefits resulting from the research;
- The responsibility principle, since according to Declaration of Helsinki, it is a duty of physicians to protect life, health, dignity, integrity, privacy, auto determination and confidentiality of individuals who participate in any clinical research (61).

4.3. Duties and Rights of Clinical Study Participants

There are a set of rights that people who participate in clinical studies should be informed about them. However, there are also some duties for participants, as well as for their family or their legal representatives, in order to do not jeopardize the research and their own security and health.

So, clinical studies participants have the right to:

- Be respected;
- Know which will happen in the study, with the possibility of questioning and obtaining satisfactory answers, before and during their participation;
- Decide about their state of health and the treatments, being able to refuse any test, medication or procedure;
- Have time to decide about the participation in the clinical study or to decide whether to continue or withdraw his/her participation at any time;
- Be informed about new benefits, risks or adverse reactions known during the study realization;

- Have knowledge about the confidentiality and security of personal data and information. Situations in which the confidentiality must be broken should be also presented to the participant;
- Be assisted and have an indemnity in case of any loss, whether or not foreseen in the informed consent. For these possible situations, it must be created an assurance that is supported by the Sponsor;
- Be clinically followed up after completion of the study (62,63).

By the other side, participants have the following duties:

- To discuss the possibility of participation with family members and/or family doctor;
- To make an informed decision about the participation in a clinical study;
- To question any doubts that is not completely clear;
- To know what is expected of the participant in the clinical study;
- To strictly follow all indications provided by research physicians and study team;
- To attend clinical study consultations, advising when it is impossible to attend;
- To maintain the research physician informed about any change that occurs during the clinical study, reporting any occurrence (a possible adverse event);
- To provide all known information about the clinical history (62,63).

4.4. Informed Consent Form

As it was discussed above, it is a right of potential participants to obtain all information that is considered relevant for their decision about the participation or not in the clinical study in order to give an informed consent. It must be also explained the right to revoke the informed consent form at any time of the clinical study. Before the participant be eligible at the study, the investigator has the responsibility to ensure that participants will voluntarily entry at the clinical study, assuming that she/he is a capable individual.

An adequate informed consent form should be provided to everyone who want to participate in the clinical study, after having been informed and understood all information given by the investigator and before to participate in any procedure inserted in the clinical study. This informed consent form is a written document specific for each clinical study and should be approved by an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) before initiating the clinical study. Paper of IRB/IEC will be discussed on the net subchapter. The following points are an excerpt of the guideline for Good Clinical Practice (GCP), a document that will be discussed latter at the present work, which establishes all information that would be present on the informed consent form, namely:

“(a) That the trial involves research.

(b) The purpose of the trial.

- (c) The trial treatment(s) and the probability for random assignment to each treatment.
- (d) The trial procedures to be followed, including all invasive procedures.
- (e) The subject's responsibilities.
- (f) Those aspects of the trial that are experimental.
- (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- (j) The compensation and/or treatment available to the subject in the event of trial-related injury.
- (k) The anticipated prorated payment, if any, to the subject for participating in the trial.
- (l) The anticipated expenses, if any, to the subject for participating in the trial.
- (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- (s) The expected duration of the subject's participation in the trial.
- (t) The approximate number of subjects involved in the trial (64)."

So, the writing, reading and signature of the informed consent must be considered as a critical step of the clinical study and not as only a signature of a document. However, in cases that clinical studies with orphan drugs, it should be given special attention to patients who suffer from those conditions and are potential participants. Once these is an opportunity

for a treatment with an innovator medicine, patients are under more pressure and the investigator must have special cautions and be certain that the potential participant are conscious about possible risks and benefits. Beyond this, the informed consent form should be written in a language appropriate to the level of understanding of the population target. For potential participants of countries in development, as countries of the Third World, all information about the clinical study and their participation should be detailed and explained with a level that is understandable to the concerned population.

4.4.1 The Informed Consent Process for Minors or Disabled Potential Participants

About half of people who suffer from rare diseases are children and, as it was referred in chapter 2, NTDs are also more prevalent in children of countries in development (17,65). For clinical studies where the population target are children or disabled adults, the process of informed consent is foreseen on applicable regulations and laws. According with Portuguese Law no 21/2014 of 16th April, named as Law of Clinical Investigation, for the participation of minors aged with sixteen years or over, it should be obtained their informed consent as well as the informed consent of their representatives (66). In case of an incapable adult or a child under sixteen years of age, the free and informed consent of his/her legal representative must be obtained, always reflecting their will (66). These legal representants should receive all relevant information about the clinical study according their level of understood. Any desire expressed by the minor or by the disable adult (e.g. to withdraw from the clinical study whatever the moment, etc.) should be attended and respected by the investigator.

Ethically, there are some doubts about the power of the legal representant decision. For this reason, clinical studies should not be carried out with minors or incapable adults when exists the possibility to be realized with adults able to give their free and informed consent.

They are only carried out with minors if:

- Exist a direct relation with their clinical condition.
- Direct benefits are foreseen for these population target.
- In cases that clinical study is designed to minimize pain, malaise, fear or other risk related to the disease (66).

The last situation is also applicable for the realization of clinical studies with incapable adults as well as when it is essential to validate the results obtained with clinical studies carried out for the same condition with capable adults (66).

4.5. Conflicts of Interest and Responsibility

The paper assumed as investigator by a physician can generate some pressure in relation to patients that participate in a clinical study, since they may feel compelled to participate on it due to fear of withdrawal of attention from the investigating physician.

The physician is confronted with various papers, each one with different responsibilities, such as the duty of protection, loyalty and help with patients, and in another hand, the duty to investigate (61).

Pharmaceutical companies, entities that most promotes the clinical research, is moved by great financial interests, demonstrating the idea that the medicine that is being tested is safe and the efficacy, through publication of positives results and omitting and undervaluing the negative results with the clinical study that was conducted (61).

With the purpose to minimize all these interest conflicts, the clinical studies should be randomized, blinded and with allowed access without restrictions to statistical results (61).

4.6. The Use of Placebo in Clinical Studies

The placebo is a drug without active substance, used as comparator of the pharmaceutical form containing the active substance to prove the clinical and toxicological effects. It is used in clinical studies that resort to the blinding or when there are symptoms or manifestations in which subjectivity should not be excluded, such as tranquilizers, hypnotics and antidepressants (61).

Since patients are randomized to receive placebo instead of effective therapy, its use in clinical studies has generated various controversies. In these types of clinical study designs, such as for rare diseases or NTDs, it should be asked if the principle of justice and the principle beneficence are being achieved.

Part of the scientific community advocates the use of placebo in clinical studies because, even when effective therapy is available, it is often no greater than the placebo, due to the methodological limitations of the controlled clinical studies (different populations and unpredictable effects).

Regarding rare diseases, placebo can be used, since on most of cases there is no another active drug for the condition in question. Furthermore, it can be used on the following situations:

- If there are doubts about the superiority of the efficacy of the test drug in relation to the placebo;
- If the available treatment has serious adverse effects;
- If the duration of the clinical study is short;

- If conditions in which its use does not cause too much discomfort or pain due to the intensity of the symptoms (e.g., allergic rhinitis);
- If no irreversible adverse reactions are expected (61).

4.7. Conduction of Clinical Studies in Countries of the Third World

Up to date, about 7 237 clinical studies were/are being conducted in the Africa continent, a number that is relatively distant from an overall of 275 397 clinical studies carried out all over the world (67). On the figure 4, it is shown the distribution of these studies within the Africa region:

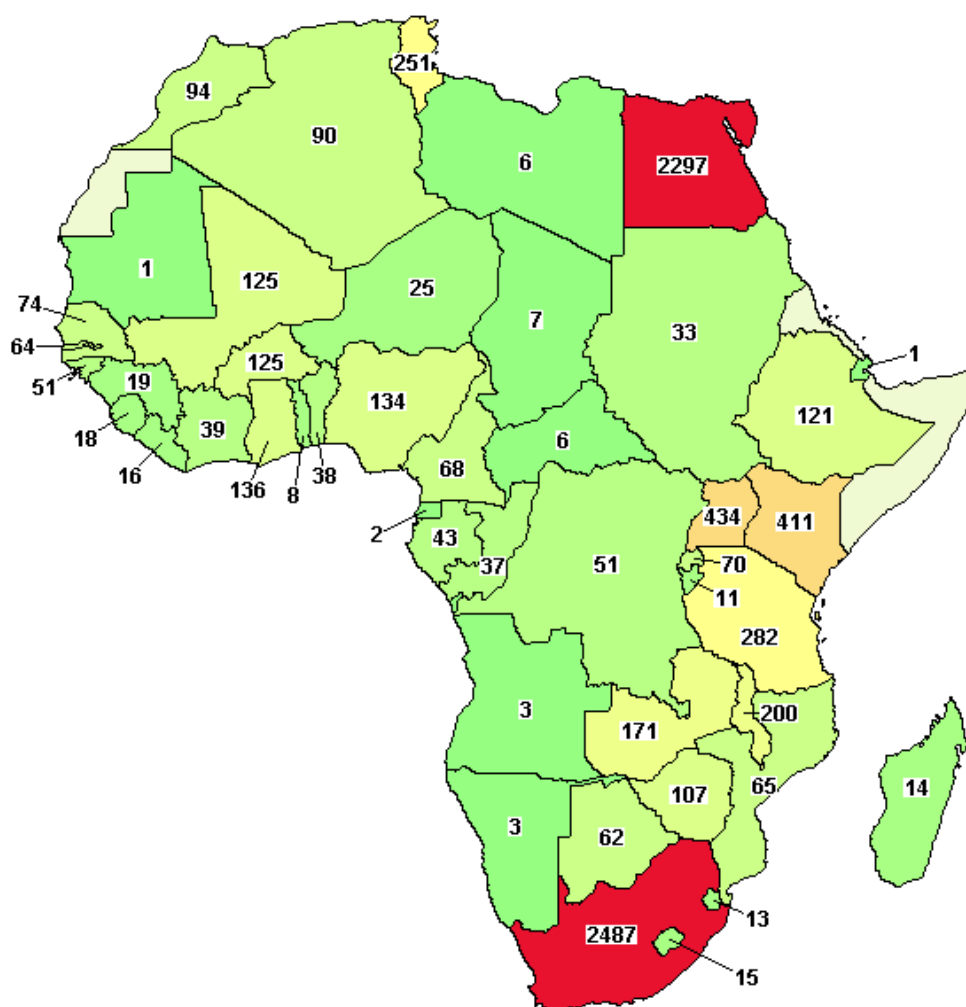


Figure 4 – Africa clinical studies distribution. Adapted from clinicaltrials.gov (67).

Analysing the figure, countries with a higher number of clinical studies are South Africa and Egypt. These numbers are completely different from the other Africa countries, which can be related with their higher organizational level and economic stability. Currently, in South Africa are being recruited participants for studies with drugs to treat many different conditions (e.g., respiratory track history, hypoxemia, smoking cessation, etc.) (67).

However, it is questioned whether the investigations carried out in Third World countries has the purpose the contribution to public health in these countries or whether it is an exploitation of these poor populations in order to benefit the developed countries. Conducting clinical studies in these countries in development is also often criticized, once participants are at risk and may ultimately not have access to the approved medicinal products (68).

Health care provided during clinical studies is always an advantage for poor populations, being sometimes the only way to have access to treatments. When the disease for which the drugs are being tested are a NTD, these situation can justify the location of the clinical study. In addition to these health benefits, clinical research in these countries can contribute to the development of local infrastructures and to improve the economy (68).

Currently, the legislation applicable plays a crucial role in the defence and protection of the most vulnerable participants. Thus, an ethical conduct depends fundamentally on the reason for conducting clinical studies in Third World countries and the informed consent of the participants, which in these cases can become a more complex task, as the population is generally less instructed.

Clinical studies resulting in the availability of new treatments and/or health care for these poor populations are generally accepted, unlike those do not offer direct or immediate benefits, questioning whether their characteristics would be accepted or not in developed countries. The last ones should be assessed on a case-by-case basis by competent authorities.

5. Clinical Studies with Orphan Drugs

A clinical study can be defined as a research carried out in humans with the purpose to answer or contributes for answering a question about human health, adding important knowledge to the society. These studies can be interventional studies or observational studies, being both discussed along this chapter. They can be realized in hospitals, health facilities or other clinical institutions (69).

The responsible for the conception of the clinical study is a Sponsor that also is the entity that supports its management and financial costs. Sometimes, these responsibilities are contracted to other entities, named as Contract Research Organizations (CROs). Generally, the Sponsor is a pharmaceutical industry, hospitals, laboratories or investigational centres (70).

Previously to the clinical study conduct, the Sponsor must contact sites in which it will be possible conducted, in order to assure that these sites have adequate human resources

and facilities to conduct it in accordance with applicable ethical and regulatory requirements (e.g. Good Clinical Practice – International Council for Harmonisation).

Regarding human resources, a Principal Investigator (usually a physician) leads the clinical study conduction and the remaining clinical team is constituted by physicians, nurses, sub-investigators (when the study is carried out in more than one site), clinical research coordinators, pharmacists and other job roles (69,70).

In this chapter it will be discussed the initial planning of a clinical study, including its design and how is made the choice of the site (s) in which they will be conducted. Along this chapter, it will be also described the possibility to conduct observational studies for orphan drugs.

5.1. Design of Clinical Studies

Before any drug be approved for use, it is required go through the clinical development phase. There are many ways for the design of a clinical study beyond the intervention strategy, as it was referred above. These design approaches are also applicable for clinical studies with orphan drugs.

Firstly, the study can be realized in only one site or in various. Furthermore, after non-clinical studies conduction, they follow a set of phases, each one with different objectives and purposes to be evaluated.

Another way to classify and design a clinical study is the randomization methodology, a process in each subject has the same statistical probability of belonging to either the control group or the group that receives the drug or intervention in study. Randomization studies can have different designs according to the objective associated with their realization, such as parallel, cross or factorial studies.

Clinical studies can be open-label or blinded for different players of the process, such as for the participants, investigator and/or clinical study coordinator.

On this subchapter it will be described each of above classifications for clinical studies.

5.1.1 Single-Site and Multicentre Clinical Studies

Single-site clinical studies are conducted by only one research team, in a single hospital centre or in health centres under its guardianship. These studies are often of small-scale and cheaper than multicentre studies. They are more frequent in phase I studies, which are generally performed in healthy volunteers, or in the evaluation of surgical innovations. Despite their easy implementation, it is difficult to draw conclusions about the differences between different groups, due to the reduced number of participants (70).

Currently, clinical studies are multicentre studies, involving participants from more than one site through a common protocol. Following the definition published on Law no 21/2014 of 16th April, the clinical study protocol is a document that describes the reasons, objectives, concepts, methodologies, monitoring, statistical approaches, organization and conduction of a clinical study (66). Generally, it is chosen a principal site to coordinate all these studies and to process and analyse the results. They are used when the sample required by the clinical study protocol is too large for its performance in only a single centre or because it would take much longer to complete the study. Since they include investigators and participants from different clinical sites, the results achieved are more reliable and representative, which allows an extrapolation for the general population with greater confidence (70).

Comparing with single-centre studies, the multicentric are more complex at the organizational level, since it is necessary to ensure that the protocol is uniformly followed. Due to the difficulty in supervising, controlling and processing data, it is essential a coordination of all sites involved, which implies constant communication between them.

5.1.2 Phases of Clinical Studies

Clinical studies are conducted in a set of steps, more known as phases. Each phase is designed to give the response for a research question. In the early stages, the drug is tested on a small number of participants in order to determine their general safety (71). In case of promising results, the number of participants increases on next phases, as it is shown on the figure 5:

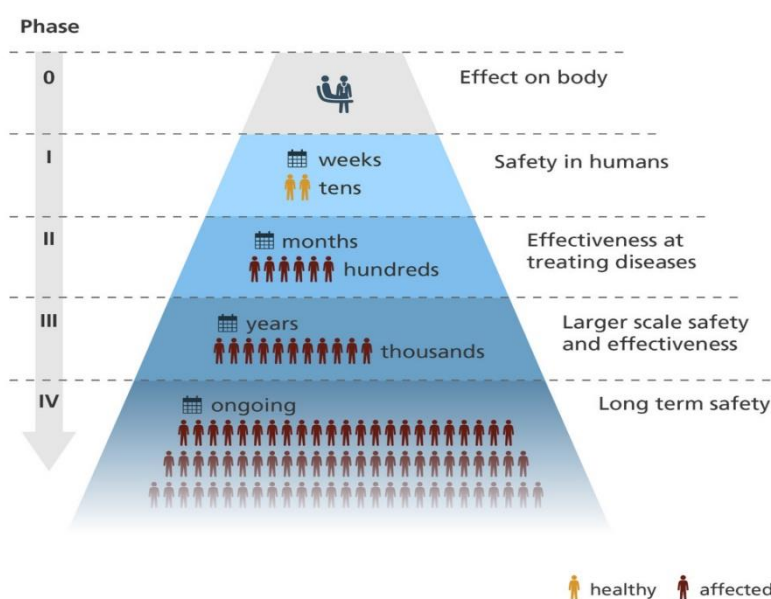


Figure 5 - Different phases of clinical studies (71). Understanding the Clinical Trial Process, 2016.

Phase I:

Prior to clinical studies, a new drug goes through pre-clinical development phase, intended to assess toxicity and determine the initial dose to be used in Phase I clinical studies (72).

Phase I studies are thus the first step on investigation of a new drug in a small group of healthy people (between twenty to one hundred participants). However, drugs with potential toxicity (e.g. cytotoxic drugs) are generally studied in patients.

With administration of single and multiple doses, it can be estimated the initial safety and tolerability of the dose range that will be used in later phases, in order to determine the nature of the adverse reactions that may occur when taking the drug (73).

Pharmacokinetic studies are also a purpose in this phase. These studies allow the clearance determination, to verify if exists accumulation of the drug or metabolites and identify potential interactions with other medicinal products (70). Information on pharmacokinetics should be obtained in special subpopulations, such as patients who suffer of renal or hepatic insufficiency, elderly, children, pregnant women, infants or in individuals of different ethnics (73). Another important parameter at this phase is to check whether food intake affects bioavailability.

The assessment of pharmacodynamics is another objective of Phase I and it is related with blood levels of the drug. In patients, if appropriate measurement is available, these pharmacodynamic data allow an estimation of activity and potential efficacy and may assist in dose determination and dosing regimen for later phases (73).

Phase II:

In phase II studies, the primary objective is to explore the therapeutic efficacy in patients, and to continue obtaining safety data to add for those obtained at the phase I (70,72). It is performed with higher number of patients (between one hundred and three hundred) that manifest the disease or condition for which the drug was developed (70).

In addition to its importance in selecting the dose and the dosing regimen for the next phase (phase III), other objectives on this phase include assessing the potential endpoints of the study, the relationship with concomitant medication and the definition of the target population for later phases (73).

Often, first studies at this stage use dose escalation to give an early dose-response estimation. Later studies, even at this phase, confirm this dose-response relationship

through the design of parallel studies with the best dose, which were previously selected (73). Phase II clinical studies are usually controlled and treatments are randomly assigned.

Phase III:

Phase III studies evaluate the therapeutic efficacy on an even larger scale and are designed to compare the new treatment with the standard treatment, if one exists. They are performed with a larger sample of patients than the previous phase (between three hundred and three thousand), representative of the target population (70).

The incidence of the most common adverse reactions should be established at this phase and, when it is possible, it should be identified the profile of patients that are most susceptible to these reactions.

On this phase, the new drug should be compared to a pre-established reference drug or a placebo, through randomized controlled studies (if possible double-blind) and following a parallel design (74).

This phase is considered the most complex, extensive and costly phase of clinical research, since it immediately precedes the commercialization of the test drug (74).

Phase IV:

After demonstrating the safety, efficacy and quality of the drug and its subsequent approval, the drug proceeds to the phase IV studies. In fact, these studies are not necessary for drug approval, but are an important step for its use optimization (73).

They are based on pharmacovigilance of the medicinal product, which includes collecting information about the adverse reactions associated with its widespread use for long periods of time (72). The most common studies at this phase are drug interactions, dose-response, safety or morbidity/mortality studies (73).

5.1.3 Randomization at Clinical Studies

The randomization is a process in which each clinical study participant is equally likely to be allocated either to the treatment group or to the control group (75). Randomized and controlled clinical studies are considered as the “gold standard” in clinical research, because they can offer the best results about efficacy of a given drug or intervention (76). Randomized studies may be classified in parallel, cross-over or factorial studies, as will be discussed in a later subchapter (75).

This type of study reduces the probability of bias in the assignment of treatment to each participant by the investigator, which allows the comparability between the groups of participants, resulting in more reliable and conclusive results (76).

All randomization techniques have advantages and disadvantages, but it is crucial that the choice lies in the technique that allows valid and interpretable results.

The randomization process can be simple, when it is based on a single sequence of random assignments, through random numbers generated by a computer or following a numerical order of a list without knowing the treatment for that each number corresponds (62,77). This approach is relatively simple to implement in clinical studies and, when they involve many participants, a simple randomization generates similar numbers of individuals between groups. Contrarily, in clinical studies with a small number of participants, this type of randomization can generate a disparity in the number of participants between groups (77).

Randomization in blocks is used for the random allocation of participants in groups that result in equal sample sizes (77). After choosing the size of the block, the characteristics of each group are pre-established and all possible combinations within the block must be calculated. This type of randomization is most commonly used when the number of participants is small, as clinical studies with orphan drugs. Although a balanced sample size can be achieved, the groups may not be comparable because of the different variables, which may introduce bias in the statistical analysis and reduce the power of the study (77).

Stratified randomization aims to control and balance the influence of factors considered relevant, preventing the treatment groups from having significant differences in the characteristics of the patients for whom the drug is tested. The investigator is responsible for a careful identification of the factors to be stratified. Thus, each block contains a combination of relevant factors and after all participants are allocated to the different blocks, randomization is performed in each block for the allocation of the participants to the different groups. This type of randomization is simple and useful for small clinical studies, but it may be difficult to control the relevant factors (77). It is also difficult to use this methodology when participants' information is incomplete at the beginning of the study.

In unequal randomization, instead of including an equal number of participants, both in the treatment group and in the control group, a greater number of subjects are attributed to the treatment group (78). It is a less frequent type of randomization but may be applicable as long as it does not affect statistical efficiency in the comparison of treatments and also in clinical studies that are comparing more than two treatments (78).

In non-randomized clinical studies, participants are allocated to the treatment or control group by the investigator through a systematic methodology, such as the day of birth, where

those born on even days are allocated to the treatment group, while the remaining will belong to the control group, or vice versa (75,78). This design presents some drawbacks, because the investigator is aware of the treatment that is assigned to each participant, which can lead to the bias of the results. On the other hand, they are easier to implement and cheaper than other designs (78).

5.1.4 Clinical Studies Methodology

A control group in a clinical study is a set of participants that receives a standard treatment, either a reference drug or a placebo.

In uncontrolled studies, only exists a test group, which may lead to erroneous conclusions about the drug that is being studied. They are used to obtain information about its best use as well as to study adverse reactions, tolerability, interactions or drug efficacy (78).

Controlled studies establish a statistically valid comparison between a group of participants that receive the test drug and a group that receive the reference drug or a placebo.

In controlled studies with an active comparator, the test drug is administered to one group of participants, and an active comparator is administered to the other group, which is usually a standard drug indicated for the disease in question.

In placebo-controlled studies, an inactive substance (placebo) is given to one group of participants, and to the other group is given the study drug.

At the end of controlled studies, either with an active comparator or with a placebo, the groups are compared to see whether the test drug demonstrates more efficacy and safety. For treatment be randomly assigned to each participant, these controlled studies are randomized (78). This type of methodology in clinical studies presents more advantages for the reliability of the results obtained about safety and efficacy.

5.1.5 Clinical Studies Specific Design

The design of the clinical study establishes the allocation of participants for different treatment groups, depending on several factors, such as the sample size or the type of pathology for which the drug is being tested (78).

On parallel studies, participants are randomly allocated to the group that receive the new drug or to the control group, and then comparing the results as it is shown on the figure 6:

Parallel Trial

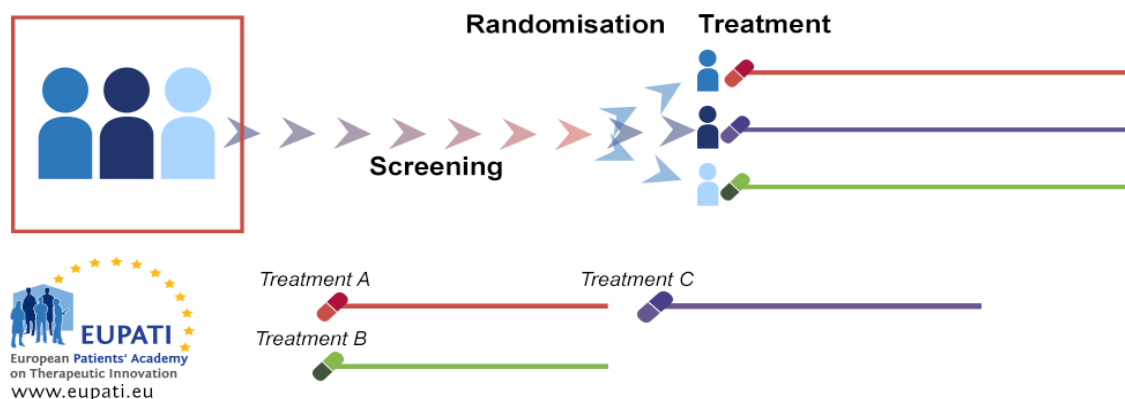


Figure 6 - Parallel design in a clinical study. European Patients' Academy, 2015 (76).

This type of design is usually used in phase III studies, since it allows the extrapolation of safety and efficacy results to general population (78). They have the disadvantage of require many participants, which prolongs the time of the conduction.

Another type of design in clinical studies is cross-over studies that is presented on the figure 7, in which each participant functions as a self-control, since they are assigned to the test and then to the control treatment (76).

The allocation to the both treatment groups occurs at different phases and the order is randomly assigned. As a main advantage, they do not require many participants to detect a statistically significant difference between the different groups.

Cross-over Trial

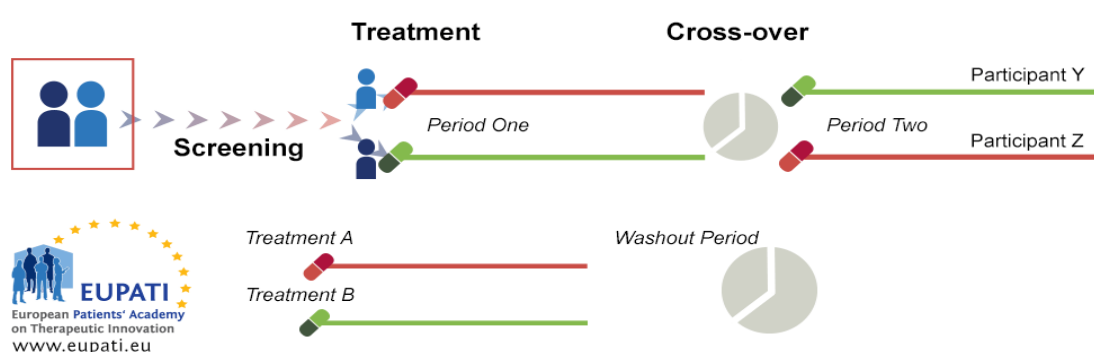


Figure 7 - Cross-over design in a clinical study. European Patients' Academy, 2015 (76).

There are variants within this type of design in clinical studies. When the first treatment does not interfere with the following, the response is evaluated in a short time interval. In case of interference between the two types of treatment, it is necessary a wash-out period between the two phases, in which occurs the elimination of the effect of the first treatment that was administered (78). However, this wash-out period should be carefully evaluated when dealing with pathologies that can not go through this intermediate stage (78). This type of design is very common in bioequivalence studies.

Randomized studies to test various treatments are known as factorial studies as shown on the figure 8. Testing more than one treatment allows to conclude about possible interactions between different treatments, represented on the figure 8 as “Active Y” and “Active X” (76).

2x2 Factorial design

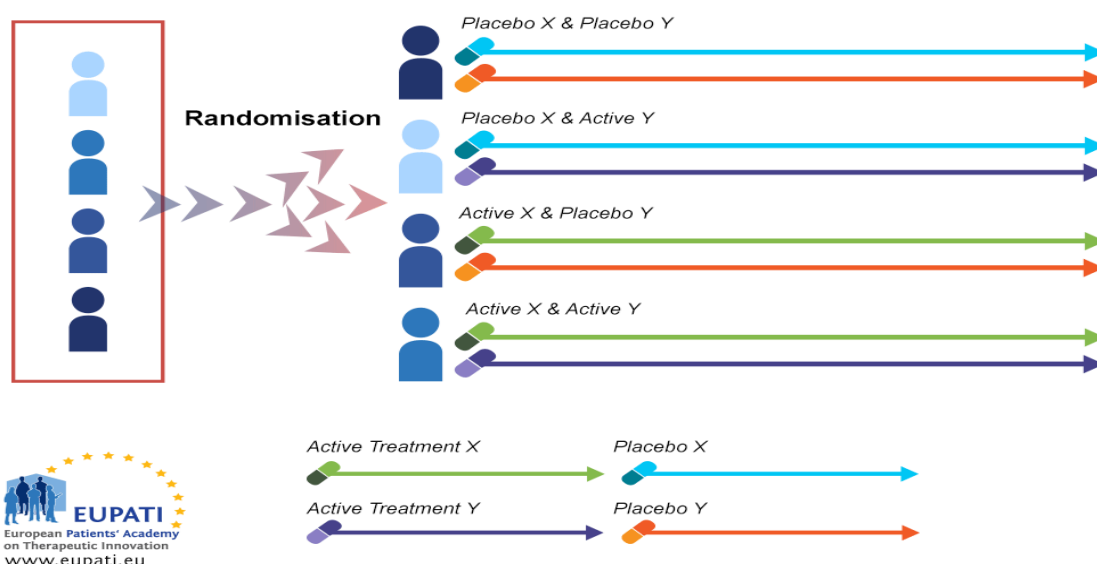


Figure 8 - Factorial design in a clinical study. European Patients' Academy, 2015 (76).

Randomized studies that match participants according with specific characteristics are named as matched pair trial studies. These characteristics or categorical variables can be for example age and gender. In each arm of the study, participants are included according with the characteristic that they have in common and within each arm, a participant receives a treatment and another participant receives the other treatment, as shown on the figure 9 (76):

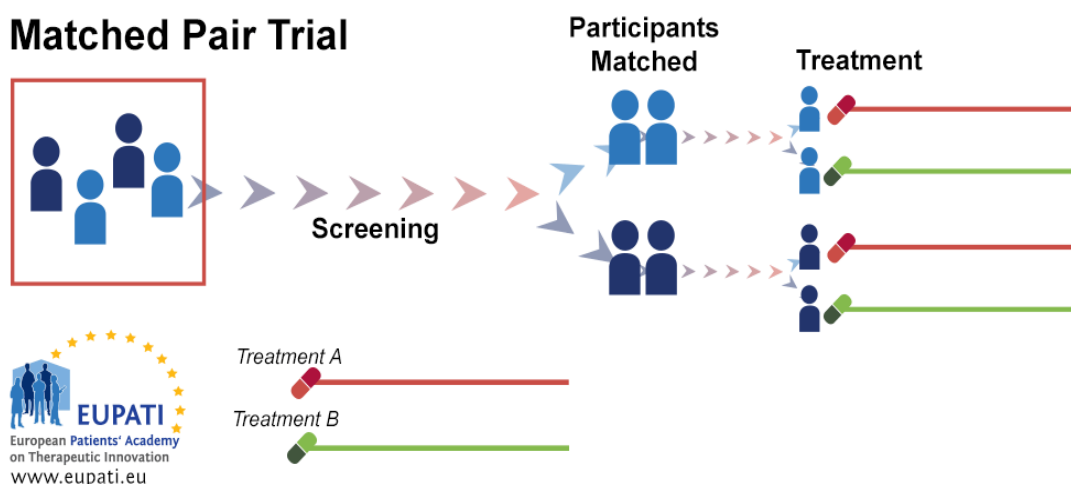


Figure 9 - Matched Pair Trial design in a clinical study. European Patients' Academy, 2015 (76).

This type of design allows the identification of the influence of two or more variables on a dependent variable (e.g. weight), which allows conclusions about the subgroup of subjects that responds better to the test treatment (78).

5.1.6 Blinding in Clinical Studies

In order to avoid influencing the response to the treatment or the cooperation of the individual with the study, producing more reliable results, clinical research may resort to the blinding of the treatment that the participant is receiving. In case of a blinding study, it can be classified as a single, double or triple blinding study.

Open-label studies are those in which all participants know what treatment or medical intervention has been assigned to them. They are most widely used in the evaluation of surgical techniques and in drug studies for the withdrawal of drugs and tobacco. These studies are easier to perform and allow a more comfortable decision for investigators, since they know the type of treatment that each participant is receiving (78).

The **simple blinding studies** are those in which the subject is unaware of the treatment group to which he/she belongs. These studies are easier to be organized and are used when it is necessary for the investigator to know the treatment that is being performed, as it is the case of cancer treatment, to better evaluate the patient's progress and to take the appropriate actions. On the other hand, this knowledge may lead to change the therapy, including dose modification or even the need for additional therapy, which will have repercussions on the evaluation of the results.

Double-blinded studies are those in which both the subject and the investigator are unaware of the treatment assigned to each treatment group. This is the preferable type of study, since it ensures objectivity and more reliable results, reducing the risk of bias. By

other side, they are more complex due to their difficult organization, since an identical pharmaceutical form should be prepared for both the placebo and the test drug, which may not be possible and with higher costs.

The investigator, the participant and the study coordinator are unaware of the treatment assigned to each group in **triple-blinded studies**, which have not present the placebo effect and the subjectivity of the investigator and the coordinator.

In case of occurrence of a serious adverse reaction, the Sponsor may break the blinding and subsequently inform the competent authority (ies) and the IRB/IEC.

5.2. Standard Process of a Clinical Study

After the design of the clinical study according with the described on above subchapters, the Sponsor or its representative (e.g. a CRO) should identify the site(s) in which the clinical study will be conducted. This process is described along this subchapter.

5.2.1 Since the Sponsor Contact until the Close-Out Visit

Clinical studies are performed after an experimental drug has been tested in pre-clinical studies.

The Sponsor or his representative (e.g. a CRO) initiates with the identification of the site (s) and investigator (s), based on their previous experience in clinical studies.

Then, the Sponsor assesses the feasibility of the study in the previously identified research centre (s): it is determined if there is the population required by the study, it is verified the investigator interest on the clinical study conduction and the conditions of the centre, in particular the availability of equipment and infrastructure. At this stage, it should be established a confidentiality agreement between the parties.

Prior to initiating the clinical investigation, a monitor - representing the Sponsor - conducts a qualification visit (also known as pre-study visit) to assess whether the investigator, team and site are capable of conducting the study according to the clinical study protocol (79). This evaluation is mainly focused on the human resources (e.g. quantity and qualifications of the site personnel), equipment, logistics and recruiting capacity of the site (79). At this pre-study visit, monitors can also view and discuss the investigator responsibilities and his/her qualifications, study purposes, informed consent process, report of adverse events, source documents, etc. (79).

Once the site and the Principal Investigator have been selected, it is necessary to state the conditions of the site where the study will take place and the process of participants inclusion for the competent authorities.

After reception of the approval to conduct the clinical study and all regulatory requirements are achieved, one or more monitors conduct a site initiation visit, which consists on the preparation of the clinical team to carry out the study according to the clinical study protocol (79). The meeting takes place at the site and ensures that everyone understands the responsibilities and procedures of the protocol, presenting guidelines and other source documents, informed consent, participant inclusion/exclusion criteria, handling of the experimental drug, the treatment of biological samples for analysis and the monitoring plan. It also aims to alert the team about potential problems that may occur during the clinical conduct and that all necessary equipment is available.

During the clinical study conduct, monitors perform periodic visits to the site, in accordance with a schedule elaborated by the Sponsor or by the CRO in order to evaluate the following items: the conduction of the clinical study, the adherence to the protocol, the documents, the safety of the participants, the accounting of the experimental drug and compliance with GCPs (79).

When the clinical study conduct of a study is completed, a close-out visit is carried out to ensure the appropriate completion of the test procedures, where all the documents involved in the study are verified and archived and the investigational medicinal product is accounted by the pharmacist (79). At these close-out visits, it is also discussed strategies and deadlines to answer the queries in order to complete Case Report Forms (CRFs), which is a paper or electronic document with information transcribed from source documents (79). The monitor is also responsible to assure that data transcribed for CRFs are legible, complete and consistent (79).

Throughout the clinical study or even after completion, audits and / or inspections may be performed. Audits are performed by suitably certified personnel designated by the Sponsor or by the site, who select the critical steps of the study for review and the documentation involved. These audits may not be announced. At final of this follow-up to the selected processes, it is collected all information in a proper document and it is made an analysis of all route causes for problems that were detected during the audit. All findings are compiled in a proper document and it can be necessary a meeting with relevant functions to present the problems, actions and the responsible (s) appointed to correct them.

Inspections may not be announced and are carried out by inspectors of the competent authorities, with the objectives of verifying the compliance with applicable legislation and regulations as well as with the clinical study protocol (s).

5.3. Natural History Studies

The natural history of a disease is the information collected about the progression of it, since its beginning until to the end, without any external intervention as a treatment (80). In its turn, a natural history study provides the collection of information along the progression of the disease, which will be cross-linked with variables that are associated with its development (e.g. genetic, environment, demographic, etc.) (80).

Because of difficulties regarding clinical studies conducted for rare diseases, competent authorities advise Sponsors to invest in evaluation of natural history of the disease, which can contribute for a more cost-effectiveness future clinical study (81). The well understanding of the rare disease can also help Sponsors (or CRO) on designing an appropriate clinical study based on the crucial information that was acquired. The draft guidance provided by FDA “Rare Diseases: Common Issues in Drug Development” appoints the information that a disease’s natural history study can add, such as:

- “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 for surrogate endpoints (81)”.

Beyond these important approaches, information collected on history studies can be used as an historic control in exceptional situations previously approved by competent authorities, such as when the disease presents a high mortality rate and the test drug contributes for its reduce (80).

Natural history studies are studies without therapeutic interventions (investigator only observes) and they can be classified as prospective, retrospective or, at the same time, prospective and retrospective (80). Retrospective studies allow to collect data for a better understanding of the natural course of the disease. However, data collected on retrospective studies can be encoded with different medical terms for the same situation, which can difficult their interpretation and contributes for less accurate and consistent conclusions. Therefore, there are information that may not be available, such as for example, medical records that were not electronically registered since patients may not

have access to the registries in a paper format, due to their follow-up on different hospitals or health centres (80).

Although the importance of retrospective studies in the collection of data for studies with rare diseases, prospective longitudinal (or long-term) natural history studies are the most recommended by competent authorities. These type of natural history studies can be carried out along of years in order to collect the maximum available information about the disease. A practice example of their application is “The International Collaborative Gaucher Group (ICGG) Gaucher Registry”, a prospective study that started on April 1991 and the estimated date for its completion is 31 January 2030. Along of these years, there were enrolled more than six thousand and five hundred patients, involving more than seven hundred sites, but it is estimated to enrol about twelve thousand patients who suffer from Gaucher disease until the end of the study (80). This observational study has the following main purposes:

- “To enhance the understanding of the variability, progression, and natural history of Gaucher disease with the ultimate goal of better guiding and assessing therapeutic interventions;
- To provide the Gaucher medical community with recommendations for monitoring patients and to provide reports on patient outcomes to help optimize patient care;
- To evaluate the long-term effectiveness of Cerezyme (82).”

Regarding currently conclusions within this study conduction there is:

- More knowledge about phenotype and genomic variability between patients;
- Important understandings that may contribute for better diagnosis and treatment of the disease;
- Understandings about the disease manifestations in children;
- Results achieved with long-term treatments;
- More knowledge about conditions that are associated with Gaucher disease (82).

However, prospective studies have some disadvantages as they can require much time to be conducted and so, it is possible that clinical study takes longer to be conducted (82). As these clinical studies directed for rare diseases do not present therapeutic advantages, because they are non-interventional studies, it should be demonstrated for patients and families (if applicable) that studies are crucial for a better understanding of the diseases and further new clinical drug developments (82).

Before the initiation of a natural history study, the clinical study objectives and related methodologies for data collection should be carefully planned, taken into account that competent authorities are available to provide scientific advice and assistance on the designing of clinical studies for rare diseases (82). During the natural history study conduction, it is important to collect more data as possible, in order to obtain outcomes

measures and appropriate biomarkers to be applied on future clinical investigations (80). Because this, monitoring activities are crucial for the accuracy of conclusions obtained from them. Although this advantages in implementing natural history studies before interventional studies, costs and time that are invested can be higher. In order to support them, competent authorities have been created programs to fund such studies, such as the FDA's Orphan Products Natural History Grants Program (80). This program launched by the Office of Orphan Products Development has the main purpose the contribution with funds for the development of drugs for rare diseases treatment through the conduction of natural history studies (80).

5.4. Clinical Studies Design for Orphan Drugs

Clinical studies that are carried out with a small number of patients present some barriers, namely:

- Pathophysiology of most of rare diseases is poor understood by medicine;
- The phenotype and genomic present higher variability;
- Lack of methods for the diseases diagnosis;
- Lack of validated biomarkers;
- Population who suffers from them are geographically dispersed;
- Research site has not sufficient experience (or none) (83).

Regarding this, poor efficacy evidences are being appointed as the limited factor for orphan drugs approval, since clinical studies for this type of diseases are only conducted on a small sample of the population. In order to improve conclusions obtained in these type of studies, EMA and FDA have been developed guidelines to help Sponsors about clinical studies design. When it is possible, randomised controlled clinical studies are the best tool to generate conclusions with a great quality (84). If it is possible to conduct different clinical studies regarding same diseases and collect conclusions, this would be the great strategy (84).

In case of rare diseases, it may not be possible to conduct various clinical studies for the same disease, but if treatment conditions and data collection methodologies are standardized, it could be a good way to provide evidences (84). Observational studies should also be considered as another option to obtain conclusions within an orphan drug. The Guideline on Clinical Trials in Small Populations refers also the importance of pre-clinical studies to obtain the maximum information in order to establish a better design for clinical studies with rare diseases. Information about dosing and route of administration should be obtained on these studies with animals or *in vitro* (84). In case of very rare

diseases, it is crucial to collect the maximum possible information on each study participant, using the best tools to analyse them (84).

Another important idea to be taken into account for the design of the clinical study with rare diseases are the choice of the endpoint (84). In these cases, a validated surrogate endpoint (i.e. biomarkers) that reflects a primary endpoint should be considered (84). Although this important evidence approach, the use of surrogate endpoints can not be the only predictive of the efficacy and it should be accompanied by other supportive evidences of the efficacy (84). A more detailed explanation about what primary endpoints and use of surrogate endpoints for generally clinical studies are described on the subchapter 5.5. Regarding the choice of the control group for clinical studies with rare diseases, on most of cases there is none treatment to use as comparator. For these cases, a placebo controlled clinical study should be the appropriate choice to demonstrate accurate results. As situations can be so different between patients who suffer from rare diseases due to their variable phenotype and genotype, an internal control should be added to the design of clinical studies (84). When an internal control is not possible, an historical control may be used, and it is only accepted the absence of any group control in cases that natural history of the disease is well known.

As the recruitment process is slower for clinical studies with rare diseases, an open sequential design can be the best option as it requires a lower number of patients to recruit and adds the possibility for a continuing inclusion of patients until to achieve a final conclusion (84).

As it was described above, it is concluded that it is not an easy process to design clinical studies with rare diseases and it is not a linear process, depending of each concerned disease. For this reason, the competent authorities provide scientific advice/protocol assistance to Sponsors (84).

Other support for this type of clinical studies that can solve various problem are digital health technologies (e.g. Internet-based communications, smart devices, mobile health technologies, etc.) (85). Generally, the costs and the schedule achievement of a clinical study is intrinsically related with the enrolment of a largest number of participants in a few number of sites (85). However, clinical studies for patients who suffer from rare diseases involve few patients and their enrolment should be done in a largest number of sites, in contrast with the other types of clinical studies (85). Digital health technologies can have an important paper through remote data collection, permitting reduce costs and to overcome distance barriers (85). Examples of this virtual challenges that can be used in studies with rare diseases include:

- Informed consent process via online meetings;

- Patient recruitment, screening and enrolment via an online disease-specific registry;
- Virtual coordination centre for the management of clinical operations and resolution of all related medical issues;
- Electronic data collection, using for example, smartphones with software applications that reports data directly to investigators;
- Virtual patients follow-up visits (85).

So, when these technologies are applied in clinical trials with rare diseases, they can contribute for:

- Maximizing recruitment rates;
- Reducing patient burden, since difficulties with travels and related arrangement are exceeded;
- Protocol compliance and improvement of participants retention (85).

The first initiative to implement a clinical study based on virtual technologies was promoted by Pfizer in 2011 (85). This pilot study was known as “REMOTE” and was pioneer in the use of an online informed consent, in capturing data electronically and remotely as well as in distributing the blinded investigational drug remotely (85). These methodologies were achieved with success, but the enrolment rate was insufficient (85). Along of years, other pilot studies were carried out using these new technologies. Sponsors are concerned in gather the necessary experience to ensure that data generated by these studies are sufficiently accurate and feasible so, it is important to continue investigations about them. Patient satisfaction, protocol compliance and the achievement of the planned time for the conduction of the study are examples of metrics that should be managed in these studies, to verify if the applied technologies improved (or not) the clinical study conduct (85).

Regarding clinical studies with NTDs, their design depends of the disease and generally, the recruitment is not a problem as in rare diseases, as NTDs affect a large amount of population at the world. Special concerns on these studies are related with ethics, as it was referred on above chapter.

5.5. Methodologies to Evaluate Clinical Studies

Any incomplete and incorrect assessment of the quality of clinical studies may jeopardize public health. Consequently, a suitable system for the evaluation of a clinical study needs to be analysed and classified as to its validity, importance and applicability in the clinical context, taking into account a possible inclusion of the knowledge generated in the target population (86). There are several assessment systems that are based on various clinical study questions, such as scales. However, the use of only one of these systems does not

prove to be sufficient and it is necessary to link several evaluation systems. This subchapter refers only two types of possible scales to use, namely the Jadad scale and the *António Vaz de Carneiro* scale.

The success of the treatment for which the clinical study was designed, can be evaluated through endpoints, thus being a parameter that allows to verify if the treatment objectives were reached during the clinical study.

5.4.1 Jadad Scale

The Jadad scale (table 3) is used to evaluate the quality of the methodology of the controlled clinical studies, considering some parameters that are included in other scales and lists of clinical study evaluation criteria (87).

This scale lists only three main methodological characteristics, namely randomization, blinding and dropouts. For the first five answers, one point is added for each "yes" answer and, for the last two answers, one point is subtracted for each "yes" answer. Thus, the final score is between zero and five. Due to its small size, the scale is easy to use.

Table 3 – Items evaluated on the Jadad Scale. Adapted from Berger, et.al, 2010 (87).

Item	Punctuation
1. a) Was the study described as randomized (includes words as “randomly”, “random” or “randomization”)?	0/1
1. b) Was the methodology used to generate the random sequence described and appropriate (table of random numbers, generated through a computer, etc.)?	0/1
2. a) Was the study described as double-blinded?	0/1
2. b) Was the double-blinded methodology described and appropriate?	0/1
3. Was there any description of losses and exclusions?	0/1
Subtract one point if the method used to generate the random sequence was described and inappropriate (patients were allocated alternately or according to date of birth, etc.).	0/-1
Subtract one point if the study was described as double-blind but the concealment method was inappropriate	0/-1

5.4.2 António Vaz de Carneiro Scale

António Vaz de Carneiro, a renowned physician and teacher at the Faculty of Medicine at the University of Lisbon, elaborated a scale that lists certain methodological issues to which clinical studies should respond. This scale is shown on the table 4.

These questions aim to:

- Analyse the validity of the study, in which its design must answer the question asked;
- Verify if the results are clinically significant in addition to being statistically os significant;
- Analyse the applicability of the results obtained to the target population (86).

Table 4 – Scale of António Vaz de Carneiro. Adapted from Carneiro, 2008 (86).

Results Validity
1. Was the range of patients well defined?
2. Were the inclusion and exclusion criteria logical and clear?
3. Was the diseases diagnosis well characterized?
4. Were the patients randomized?
5. Was the randomization method well explained?
6. Was the distribution blinded?
7. Were the patients analysed on the groups for which they had been initially randomized (intention to treat)?
8. Was the sample size statically calculated?
9. Were the patients in the comparison group similar in terms of their known prognostic factors?
10. Except for the study treatment, were all patients treated in the same way?
11. Was blinded to patients the group to which they belong?
12. Were blinded to the investigators the study groups?
13. Were the study groups blinded to data analysers?
14. Was the final follow-up higher than 80%?
Results Significance
15. Was the size of the therapeutic effect important?

16. Is the estimate of the effect accurate enough?
17. Have this effect clinical significance?
Results Applicability
18. Are the study patients similar to those of the individual physician's practice?
19. Were considered all important clinical findings?
20. Do the treatment benefits outweigh potential risks and costs of implementation?

Each question can be classified into:

- Affirmative answer (equivalent to a "yes") where two points are awarded;
- Unclear (possible) answer that equals one point;
- Negative answer (equivalent to a "no") in which zero points are awarded;
- Not applicable.

The *António Vaz de Carneiro* scale has a total of twenty questions, which after being answered, the final score is calculated. Clinical studies with a rating of 75% or more are considered to have good quality. All the others may be considered excluded since they have not sufficient quality to be considered in clinical practice.

5.4.3 Selection and Evaluation of Clinical Endpoints

An endpoint is a parameter that can be compared between different groups in a clinical study in order to evaluate the success of the treatment. In this way, results must be defined and quantified in a prospective and unambiguous way, which corresponds to the scientific objectives of a clinical study (88). Primary endpoints are the main result obtained at the end of a study and can be classified into true endpoints or surrogate endpoints.

True endpoints are those that have a direct clinical significance in the patient, such as mortality or remission of cancer. In cases where obtaining a true endpoint is too expensive in terms of time and costs, or when it is difficult to measure, surrogate endpoints are used. At this type of endpoint, treatment-induced changes should be reflected in a measurable clinical change.

Surrogate endpoints have several advantages, namely their lower cost, the possibility of reducing the size of the sample and the time required to perform the clinical, as it was also referred about their use for clinical studies with rare diseases. Examples of these markers are hypertension associated with an increased risk of heart failure or stroke, or hypercholesterolemia, a risk factor for the development of atherosclerosis (88).

6. Pharmacoeconomic Assessment in Orphan Drugs

Pharmacoeconomics is a pharmaceutical area with the objective to allocate resources to maximize population health when using medicinal products (89).

Regarding any market with a small population target, the cost of product/service development is generally higher than other markets in which the product/service is directed to a higher number of users (5). Example of a market niche is the orphan drugs production, where costs can reach hundred thousand dollars/ euros by year for each patient who suffer from an orphan disease (5). In case of NTDs, due to their location in poor locations, investments by Sponsors are also lower as the return is not foreseen. Since the development and issuance of the Orphan Drug Act in USA and the Regulation (EC) No 141/2000 in Europe, many countries have been created their proper legislation in order to contribute to the development of new drugs for orphan diseases treatment. Incentives provided by FDA and EMA have been essential for all new developments in orphan drugs, being that the market exclusivity provided by both is considered as the principal pioneering (5). However, this incentive is only effective posteriorly to the clinical development phase of the drug and at this time, EMA and FDA can provide other key incentives, as protocol assistance and reduced regulatory fees (5).

In this chapter, it will be presented an economic overview of this specific market, discussing the value of orphan drugs for the society and Sponsors. Furthermore, it will be discussed individual national incentives for orphan drug development, created and implemented by some European countries, including Portugal.

6.1. Health Economic Assessment for Orphan Drugs

The number of new orphan drugs approvals in USA and Europe are being improved since the issuance of regulations related with orphan diseases, as the Orphan Drug Act and the Regulation (EC) No 141/2000, as it is shown on the figure 10 (90):

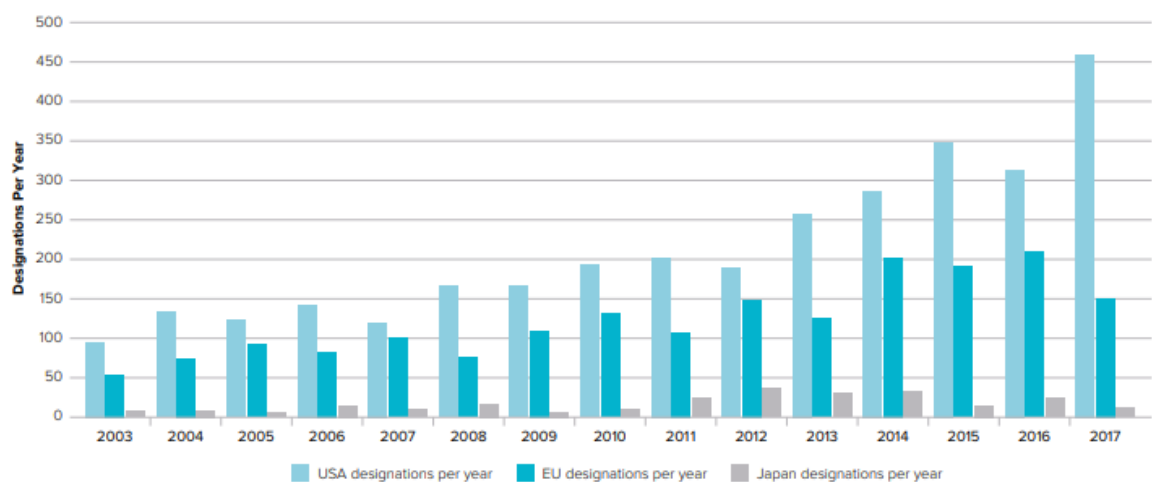


Figure 10- USA, Europe and Japan orphan designations per year (2003-2017). Evaluate Pharma, 2018 (90).

Based on the figure 10, it is possible to see that FDA has approved more orphan drugs than EMA for the same period of time, which can be justifiable with the fact that the Orphan Drug Act had been issued seventeenth years early than Regulation (EC) No 141/2000. Furthermore, these differences can also be related with incentives provided by each competent authority. By other side, Japan do not present a solid behaviour for orphan designation approvals.

The increase of new orphan drugs approval leads to higher sales and consequently, more gains to the pharmaceutical companies responsible for their development. A recent report issued by a company that evaluates the pharmaceutical market trends shows that in 2017, the sales of orphan drugs represents about 16% of the worldwide pharmaceutical market. The same report also foreseen that these sales will increase to 21,7% of the worldwide prescription sales until 2024, which is equivalent to two hundred and sixty two billions of dollars (90). This fast growing of the orphan drug market is shown on the figure 11:

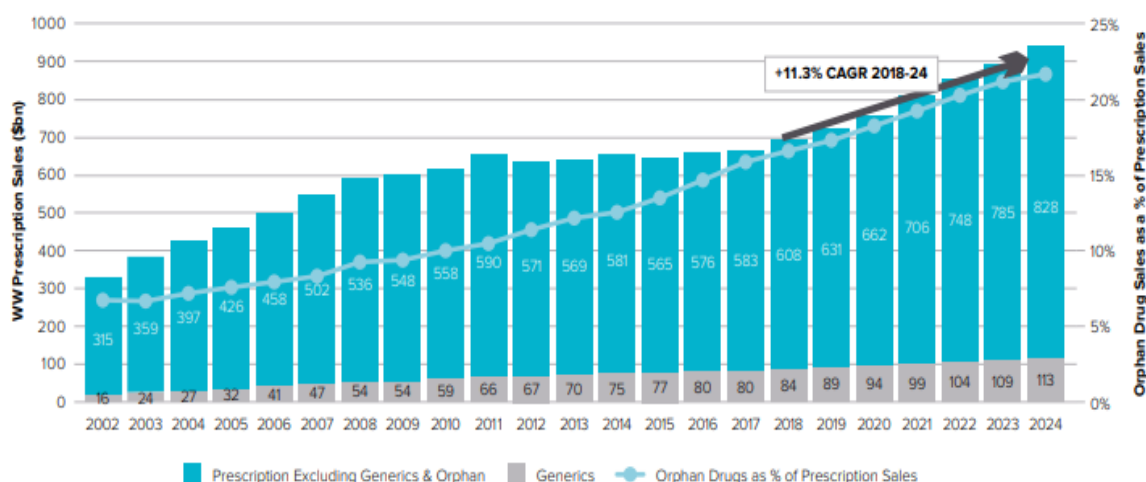


Figure 11 – Worldwide orphan sales compared with non-orphan drugs market. Evaluate Pharma, 2018 (91).

The figure 11 also shows the progressive growing up of the generics market, which currently represents a substantial part of the worldwide prescription sales (90).

However, the growth of orphan drugs market signifies major expenses supported by governments, which are a controversial theme due to their significant costs, when compared with non-orphan drugs market. A patient who suffer from an orphan disease in USA has a median cost of 84 062 dollars per year, which means more 68 253 dollars (about 85%) than what is expensed with patients who suffer from non-orphan diseases (90). These differences are shown on the figure 12:

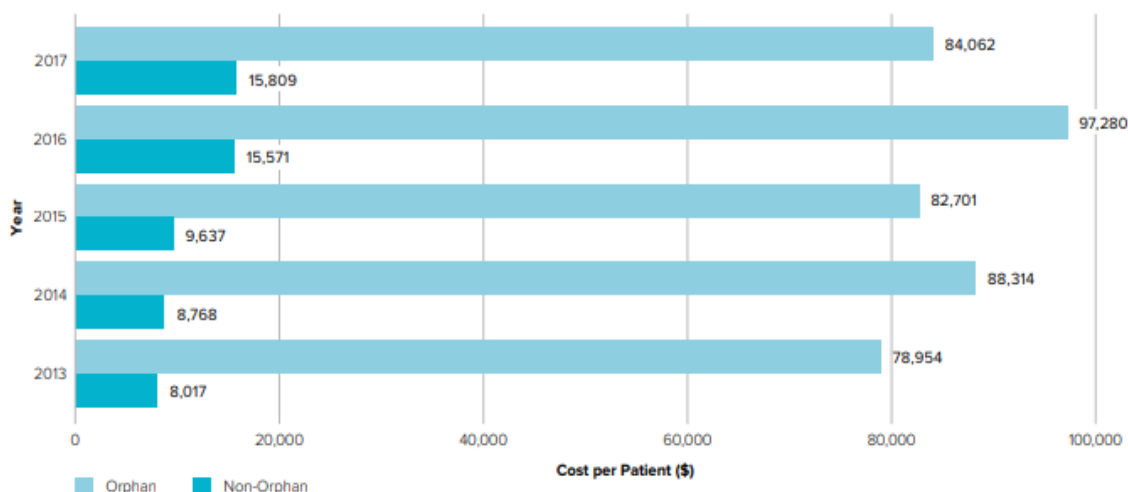


Figure 12 – Median cost per patient per year, based on the top one hundred drugs in the USA (2013-2017). Evaluate Pharma, 2018 (91).

The figure 12 shows also that median costs with orphan drugs decreased from 2016 to 2017, maybe due to the pressure that is being made with Sponsors of new orphan drugs. By other side, costs with the other patients suffer a slightly increasing because the existent gap between these two different type of drugs (90).

In order to comprehend the real social value of orphan drugs, different approaches are appearing in discussion based on the classic utilitarian doctrine and also in an egalitarian approach (56). Regarding health context, the classic utilitarian vision defends that benefits achieved with a certain treatment should be extended to the greatest number of patients who suffer from the disease, meaning that the balance between the cost-benefit has not the same importance (56). Based on this vision, the benefits are generally evaluated based on the quality-adjusted life-year (QALY) or another relevant measure for the specific disease (91). However, limits are applied to give QALYs, such as the example of the United Kingdom, where health innovations that requires more than thirty thousand dollars to reach a QALY requires other valid reasons to be funded by the health system (91). This principle is easy to understand, but other similar metrics are accepted, as for example the disability-adjusted life years (DALY) that represents the numbers of years lost due to a disease (92). However, this cost-effectiveness based on formulae present some limitations as the following:

- The interval previously defined to reach a QALY does not have in consideration the inflation;
- The QALY and DALY differentiates the treatments according to patients age, given preference to the treatment of young people;
- Do not take into account the economy resulted from an early and effective treatment;
- Do not take into account the social value, such as the equal opportunity to receive the treatment, a vision defended by the egalitarian doctrine, as it will be discussed later;
- QALY can prejudice the economic evaluation of orphan drugs, since these of drugs are seen historically as cost-ineffective;
- An economic assessment of any drug based on the all types of contributions for human health reduces human life to a price (92).

In contrast to the classic utilitarian vision, an egalitarian doctrine defends the equality in the distribution of benefits where the ratio cost-benefit is predominant on the assessment of orphan drug costs support (56). From these two different points of view, the last one is in the same line that what is requested on regulations issued by competent authorities about orphan drugs. This approach also justifies the support that is been given by governments with the purpose to improve the funds provided for orphan drugs development. The literature shows that there is not yet a consensual agreement about what should be considered on the effectiveness and economic evaluation, and from there, the applicable reimbursement decisions made by governments.

However, any measure considered for an economical evaluation of a given drug, should not be considered as sufficient for a final decision. The assessment should also compare the referred drug with a drug reference already funded by the national healthcare system or using a defined interval of money payed by each unit of health gained, as it was referred above (91).

But following strictly the first criteria, a new orphan drug would not be never funded in the United Kingdom, which permits to conclude that this assessment mode can not be used on the economic evaluation of these type of drugs.

As pharmaceutical companies have the objective to be recovered with all costs invested on research and development of orphan drugs and target population is small, costs by patient treatment will be considerable higher. As it was discussed on later chapters, the clinical development is usually less conclusive when compared with the other drugs, which also increase uncertainties of decisions-makers during its economic evaluation (91).

In order to solve the problem of the economic assessment of new orphan drugs, some countries have developed mechanisms additional to the cost-effectiveness assessment. In addition to the need of more arguments to validate a request for a drug with a cost higher than thirty thousand dollars in United Kingdom (the example referred above), this government directs the assessment of the costs of expensive treatments by the National Institute for Health and Clinical Excellence, with the purpose to give a more transparent final decision about the related drug (92).

6.2. Specific Countries Incentives for Orphan Drugs Development

Beyond general incentives foreseen by regulations on orphan drugs development, European countries are concerned in the creation of proper incentives to contribute for its development. The EC collects this information next to each national competent authority, through the delivery of proper questionnaires (6).

Firstly, specific measures directed to research and development are being implemented in some European countries, as reduced fees, public funding and scientific and regulatory support in this early phase. Some countries are also allowing patients treatment with orphan medicinal products that have not being authorized yet at the market, with the condition of a responsibility be stated by physician or Sponsor (6). Specific incentives more differentiate examples provided by each European country are described below.

Belgium is a practice example of support given to research and development phase, since advanced with an agreement with **Netherlands** and **Luxembourg**, which has the objective to increase the potential of negotiation next to the Sponsors (6).

Bulgaria follows the example that was referred above, permitting the administration of an unauthorised orphan medicinal product since given by specialized physicians. Public funding for orphan drugs development is provided by Ministry of Health that is directed for diseases not covered by insurances and also by a proper national insurance (6). A similar example is **Denmark**, but the offered treatment can only be given in specialised hospitals. The access to any orphan drug is free of charges (6). This country also promotes and developed a strategy with help of patient organizations and other stakeholders concerned in rare diseases (6).

Czech Republic supports regulatory fees and the economic evaluation and reimbursement of expenses related with orphan drugs are a responsibility of the “Act on Public Health Insurance” (6). This example shows a concerned by this country in maintain transparency on economic assessment of these type of medicinal products.

Estonia represents a different mode of incentive, facilitating the process of submission for the reimbursement, through the possibility to deliver the application without being translated (6).

In **France**, beyond the exemption of tax applications, scientific advices are also free of charge for orphan medicinal products (6). The early access to orphan medicinal products can be available to patients before their marketing authorization. But this country has another key incentive: in the negotiation of orphan prices with Sponsors, for those which represents more than fifty thousand euros per patient by year, the company has to ensure that treatment will be always available for all patients that need of them and annual sales achieved have an upper limit (6).

In **Germany**, the national health insurance reimburses directly all orphan medicinal products after their marketing authorization (6).

Greece developed a national rare diseases plan and beyond general incentives, has a different methodology for the attribution of prices to the orphan drugs. Prices for new medicinal products are given every four months and it is based on the price given by another two Member States (6).

Ireland is an example of the investment on research in rare diseases (6). A similar example is **Italy**, where scientific advices regarding orphan drugs have a discount of 50% on applicable fees (6). A special fund is also granted by the Italian government for orphan drugs that are waiting for approval (6).

Academic trials have special incentives in **Malta**, being reduced with 70% of fees (6).

Netherlands represents a country with many incentives for the orphan drugs development: registration is free of charges, tax reduction in research and development

provided by start-ups and the possibility to administer an orphan drugs not approved yet (6).

In contrast with all previous referred examples, **Poland** do not have special incentives for orphan drug development and decisions about reimbursements are decided case by case by Minister for Health (6).

Slovakia has a specific reimbursement process for orphan drugs: during two firstly years the medicinal product is reimbursed and then, the reimbursement applicability will be evaluated again (6).

Spain created the Carlos III Institute of Health, a specialized entity financed for the research and development of new orphan medicinal products. This country is also concerned with the scientific support and developed a webpage to facilitate applications processes. This webpage shows all status of authorisations realised in Spain (6).

As the last European practice example, the **United Kingdom** provides free scientific advice support and the possibility of an early access to a non-approved orphan medicinal process, after a previous analysis given by the Medicines and Healthcare Products Regulatory Agency (6).

The table 5 shows the total fees reductions provided by Europe for processes related with new orphan medicinal products development:

Table 5 – Total of fee reductions processed in Europe. European Commission, 2015 (6).

Year	EUR	Year	EUR
2000	699 500	2008	4 767 500
2001	1 297 500	2009	6 347 200
2002	2 407 500	2010	6 742 800
2003	2 814 100	2011	4 719 605
2004	3 988 700	2012	7 490 720
2005	6 842 900	2013	6 677 360
2006	6 716 450	2014	9 432 260
2007	4 892 000	2015	13 228 960
		Total	78 359 905

Analysing data provided by the table 5, it can be concluded that the support given to new orphan drugs are increasing each year, a proof that there are many significant efforts done by Europe Member States regarding the development of new therapies for the treatment of orphan diseases.

6.3. The Portuguese Example regarding Orphan Drugs Development

In **Portugal**, it is estimated that currently more than six hundred thousand people suffer from rare diseases. Orphan drugs are mostly dispensed in hospitals and patients do not have to pay anything by the treatment. When the orphan medicinal product is not authorised in Portugal, the hospital requests it to the INFARMED, I.P., the national medicines agency (6). This authority makes part of Portuguese Minister of Health and is responsible for the evaluation, authorisation, inspection and manufacture control, distribution, marketing and use of human medicinal products in Portugal (93).

Each patient who suffer from a rare disease receives an identification card that allows an easy attendance to the patient in case of emergency situations, making available all relevant information about the condition of the patient (6,94). The figure 13 shows the evolution of requests of these identification cards:

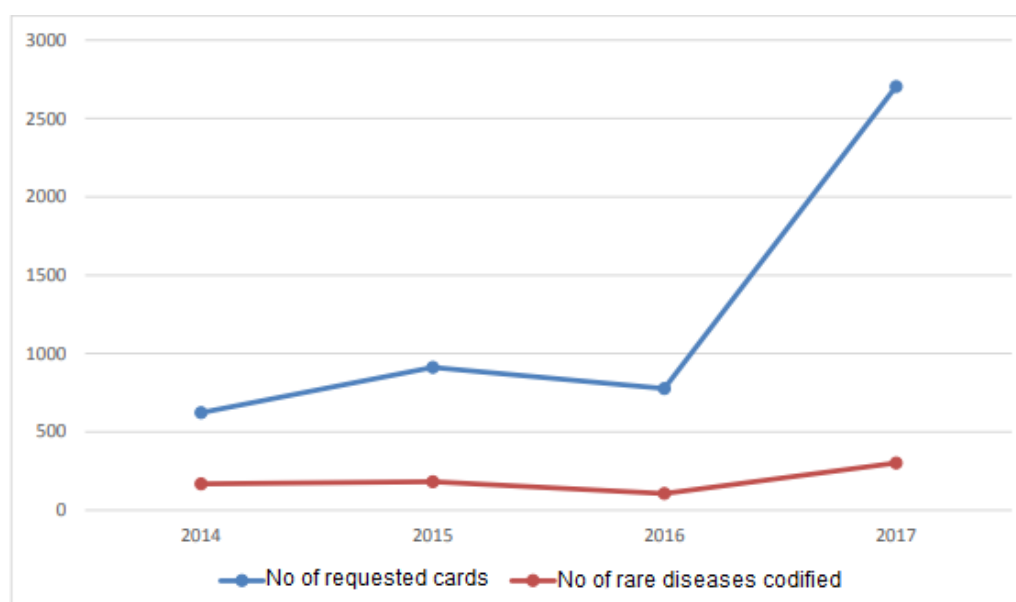


Figure 13 – Evolution of the identification cards requests (2014-2017). Adapted from *Direção Geral da Saúde*, 2018 (94).

Regarding figure 13, it is possible to conclude that the number of people diagnosed with a rare disease in Portugal is increasing, also accompanied by a growing of the number of rare diseases codified (94). Other relevant data published in a *Direção Geral da Saúde* report reveals that cystic fibrosis, haemophilia A, familial amyloid polyneuropathy and phenylketonuria were rare diseases for which an higher number of identification cards were requested (94). This fact can signify that these are rare diseases more prevalent in Portugal.

In a recent press release, INFARMED I.P. exposed that it was invested more than ninety million euros in 2017 for treatments with orphan drugs, as it is shown on the figure 14 (95).

Recent numbers published by INFARMED, I.P. about the monthly expenses in Portuguese hospitals with medicinal products demonstrate that between January and April

of 2018 it were expensed with orphan drugs about forty-five million euros, representing 10,9% of the total expended by public hospitals (96).

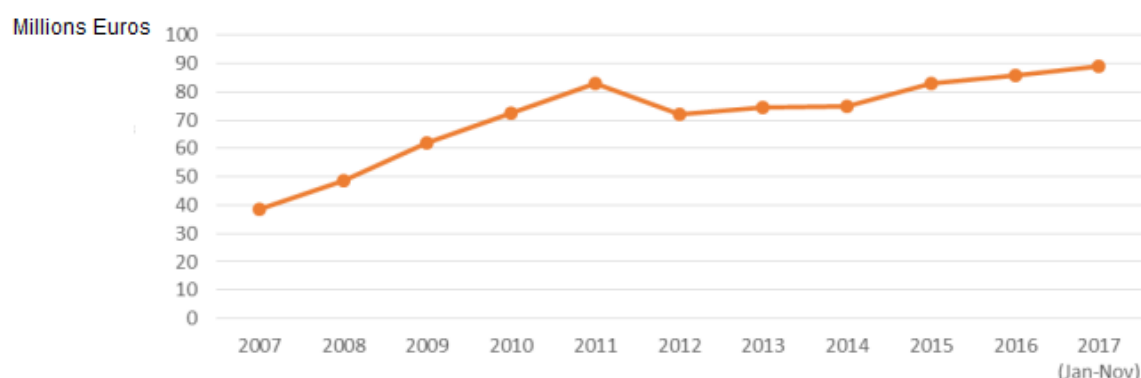


Figure 14 – Investments done by Portugal on the treatment of rare diseases (2007-2017). Adapted from INFARMED,I.P., 2018 (95).

The figure 15 shows that increasing on investments are also accompanied with an increment of orphan drugs authorised in Portugal for use by patients who suffers of rare diseases:

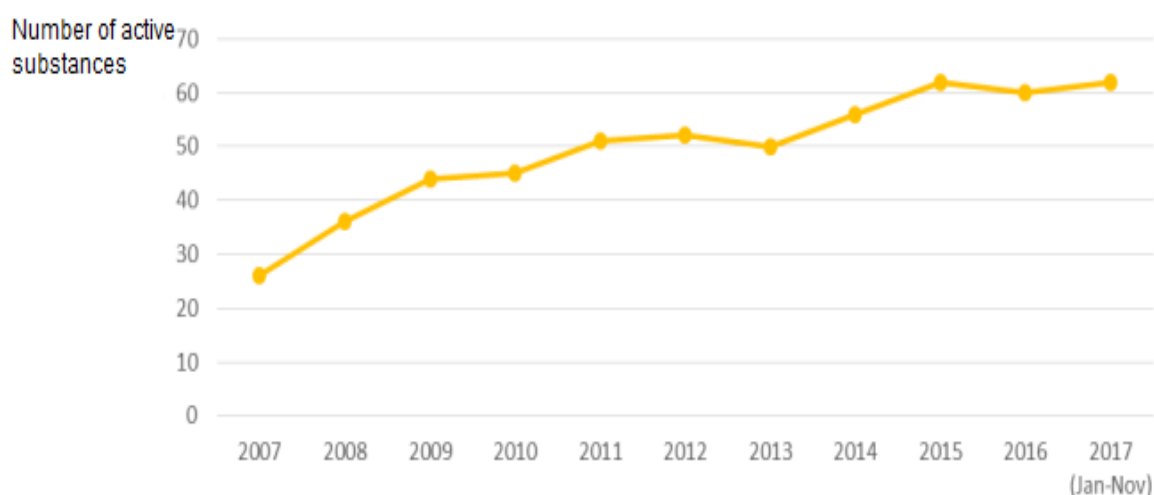


Figure 15 – Number of active substances used in Portugal for the treatment of rare disease (2007-2017). Adapted from INFARMED,I.P., 2018 (95).

The two figures below show the increased efforts that are being done by the Portuguese government in order to make available all these therapies, ensuring increasing expenses for these treatments. There are also a number of orphan drugs approved in EU that are not used in Portugal, because they were not prescribed for any patient or because do not exist any case of the disease diagnosed in Portugal (95).

Regarding expenses by each rare disease in Portugal, last data made available by INFARMED I.P. is shown on the figure 16:

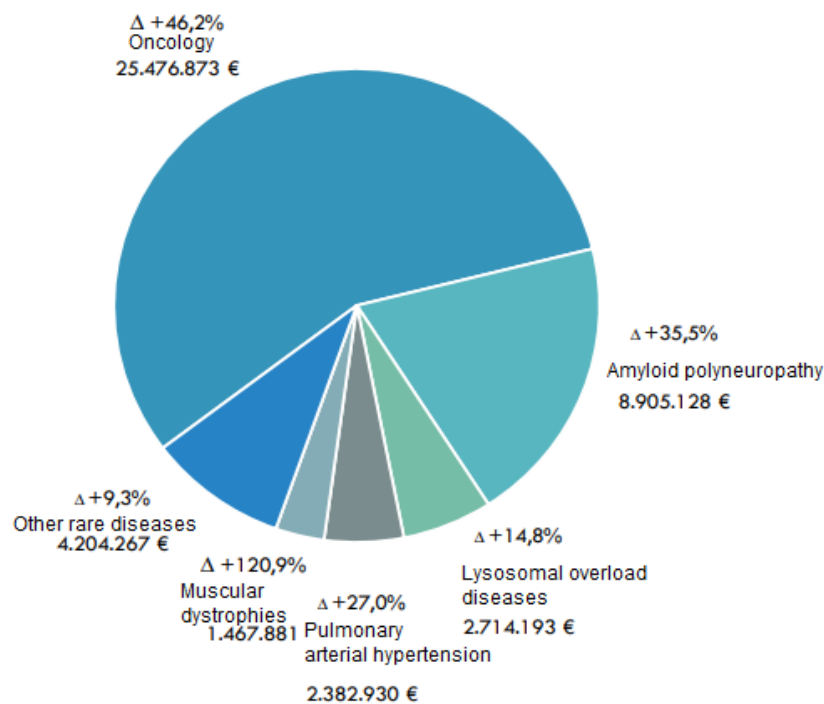


Figure 16 – Expenses with rare diseases by Portuguese public hospitals between January and April of 2018. Adapted from INFARMED, I.P., 2018 (96).

The figure 16 shows that the major part of Portuguese hospital expenses is directed for oncology treatments (96). The growing of 120,9% with expenses directed to muscular dystrophies is justifiable with the approval of the drug Ataluren, administered for the treatment of muscular dystrophy of Duchenne/Becker (96).

Similar to other countries appointed above, it is also possible in Portugal the early access to a treatment for rare disease for which the orphan drug was not approved yet and in 2017 were treated three hundred and ninety-eight patients under these special conditions (95).

7. Conclusions

Orphan diseases continue to affect many people around of the world. In most of cases, these diseases are disabling and diminish the average life expectancy. Sometimes, when the cause of a rare disease is genetic, many members of a unique family are affected. If this do not happen, family is also affected with all burden regarding difficulties on access to an effective treatment, when any exists.

Lack of effective diagnosis methodologies and inexistence of treatments for orphan disease leads competent authorities, as EMA and FDA, for the development and issuance of regulations. Firstly, the Orphan Drug Act in USA and then the Regulation (EC) No 141/2000 in Europe, had the principal purpose to incentive pharmaceutical Sponsors on the development of new diagnosis methodologies and effective treatments for the treatment of orphan diseases. These incentives are similar within the two regulations, presenting some differences relatively to the duration of the marketing authorization extension and some supports given during the clinical phase of the development of the medicinal product. Both regulations have had a positive effect and numbers of new orphan drugs approved during last years reflect it.

However, this is not an easy process on orphan diseases: as the number of target population is small or their location is on poor countries, the design of the clinical phase of the orphan medicinal product had many barriers. In case of rare diseases, as the target population is small, other type of clinical studies can contribute for a more cost-effective investment, developing natural history studies that allow the collection of information to be used latter on the design of interventional clinical studies.

Although all efforts provided by competent authorities, Sponsors and patients organizations, many ethical considerations remain concerning the access to the treatments. Other ethical concerns remain on the design and methodologies followed on clinical studies.

Regarding pharmacoeconomic evaluation of new orphan medicinal products, it is essential the development of new methodologies to be used on the assessment of new orphan medicinal products, in order to achieve an ethical distribution of new treatments, independently of their costs and number of target population.

In Portugal, the government has providing many incentives regarding rare diseases treatment. The monthly numbers published by INFARMED I.P. relatively to expenses with orphan medicines shows a great level of transparency and it is possible to conclude that it is being invested more and more money to make possible the access to these treatments by patients who suffers with rare diseases. The creation of the identification card is also an example of innovation and preoccupation by Portugal in to make available the better treatment.

Many rare diseases still without an available diagnosis technique and/or an available treatment and thousands of people who suffer from NTDs still die every day, which signify that incentives and support given by competent authorities are not sufficient yet. So, it is essential that governments of each country have increasing their concerns about the development of new methodologies capable to incentive Sponsors to develop more orphan medicinal products.

8. Bibliography

1. Murphy M. Rare Diseases: Meeting the Unique Challenges of Orphan Drug Development. Applied Clinical Trials [Internet]. 2016; Available from: <http://www.appliedclinicaltrialsonline.com/rare-diseases-meeting-unique-challenges-orphan-drug-development>
2. Health NI of. FAQs About Rare Diseases [Internet]. 2017 [cited 2018 Oct 21]. Available from: <https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases>
3. European Comission. Rare Diseases [Internet]. Policy. [cited 2017 Dec 2]. Available from: https://ec.europa.eu/health/rare_diseases/policy_en
4. Herder M. What Is the Purpose of the Orphan Drug Act? PLoS Med [Internet]. 2017;14(1):1–4. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5207521/>
5. Hall AK, Carlson MR. The current status of orphan drug development in Europe and the US. Intractable Rare Dis Res [Internet]. 2014;3(1):1–7. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4204542/pdf/irdr-3-1.pdf>
6. European Comission. Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products [Internet]. 2015. Available from: http://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_inv_report_20160126.pdf
7. European Medicines Agency. Committee for Orphan Medicinal Products (COMP) [Internet]. [cited 2018 Feb 3]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp
8. Wechsler J. Orphan Drug Surge Raises Regulatory and Development Challenges. Appl Clin Trials [Internet]. 2017;26(4). Available from: <http://www.appliedclinicaltrialsonline.com/orphan-drug-surge-raises-regulatory-and-development-challenges>
9. Ogorka T, Chanchu G. Researchers Conduct NH Studies for Rare Diseases and Drug Development. Appl Clin Trials [Internet]. 2017; Available from: <http://www.appliedclinicaltrialsonline.com/researchers-conduct-nh-studies-rare-diseases-and-drug-development>

10. WHO. Constitution of the World Health Organization: Principles [Internet]. About WHO. [cited 2018 Feb 3]. Available from: <http://www.who.int/about/mission/en/>
11. Medical Definition of Orphan disease [Internet]. Medicinenet. 2016 [cited 2018 Feb 3]. Available from: <https://www.medicinenet.com/script/main/art.asp?articlekey=11418>
12. Orphan disease [Internet]. The American Heritage® Medical Dictionary. 2007 [cited 2018 Feb 3]. Available from: <https://medical-dictionary.thefreedictionary.com/orphan+disease>
13. Breining G. Rare Diseases Difficult to Diagnose, Cures Hard to Come By [Internet]. Association of American Medical Colleges. 2017 [cited 2018 Mar 11]. Available from: <https://news.aamc.org/research/article/rare-diseases-difficult-diagnose-cures-hard-come/>
14. Orphanet. Prevalência das doenças raras: Dados bibliográficos [Internet]. Por ordem decrescente de prevalência ou número de casos publicados. 2016. Available from: http://www.orpha.net/orphacom/cahiers/docs/PT/Prevalencia_das_doencas_raras_por_prevalencia_decrescente_ou_casos.pdf
15. National Institutes of Health. Frontonasal dysplasia [Internet]. Genetic and Rare Diseases Information Center (GARD). [cited 2018 Feb 19]. Available from: <https://rarediseases.info.nih.gov/diseases/2392/frontonasal-dysplasia>
16. Roy P. Somatostatinomas [Internet]. 2015 [cited 2018 Feb 27]. Available from: <https://emedicine.medscape.com/article/182841-overview#a4>
17. Mitra AK, Mawson AR. Neglected Tropical Diseases: Epidemiology and Global Burden. *Trop Med Infect Dis*. 2017;2(36):1–15.
18. Uniting to Combat Neglected Tropical Diseases. Neglected tropical diseases [Internet]. [cited 2018 Mar 4]. Available from: <http://unitingtocombatntds.org/ntds/>
19. Field MJ, Boat TF. Rare Diseases and Orphan Products. Accelerating Research and Development. Washington: Institution of Medicine of the National Academies; 2010. 147-173 p.
20. World Health Organization. Why are some tropical diseases called ‘neglected’? [Internet]. Online Q&A. 2012 [cited 2018 Mar 6]. Available from: <http://www.who.int/features/qa/58/en/>

21. National Institutes of Health. What was the Human Genome Project and why has it been important? [Internet]. Genetics Home Reference. 2018 [cited 2018 Mar 11]. Available from: <https://ghr.nlm.nih.gov/primer/hgp/description>
22. FACES [Internet]. The National Craniofacial Association. [cited 2018 Mar 12]. Available from: <http://www.faces-cranio.org/home.html>
23. Peeling RW, Boeras DI, Nkengasong J. Re-imagining the future of diagnosis of Neglected Tropical Diseases. Comput Struct Biotechnol J [Internet]. 2017;15:271–4. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5358522/>
24. Neglected tropical diseases [Internet]. World Health Organization. 2017 [cited 2018 Feb 4]. Available from: http://www.who.int/neglected_diseases/diseases/en/
25. Hopkins A. Treating neglected tropical diseases. Community Eye Heal J [Internet]. 2013;26(82):26–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24023399>
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3756644>
26. European Medicines Agency. Pre-authorisation guidance [Internet]. Marketing authorisation. [cited 2018 Apr 8]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000167.jsp&mid=WC0b01ac0580b18196
27. European Parliament and, Council U and. Regulation (EC) No 141/2000 on orphan medicinal products [Internet]. Official Journal of the European Communities Belgium; 2000 p. 1–5. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2000_141_cons-2009-07/reg_2000_141_cons-2009-07_en.pdf
28. Comission of the European Communties. Commission Regulation (EC) No 847/2000 [Internet]. Official Journal of the European Communities Belgium; 2000 p. 5–8. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf
29. European Comission. Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000 [Internet]. Brussels; 2008. Available from: https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/c_2008_4077_en.pdf
30. FDA. Orphan Drug Regulations: Regulatory History [Internet]. Developing Products

- for Rare Diseases & Conditions. 2017 [cited 2018 Apr 17]. Available from: <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm356481.htm>
31. FDA. Orphan Drugs Regulations. Fed Regist [Internet]. 1992;57. Available from: <https://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/UCM365136.pdf>
32. Food and Drug Administration (FDA). Orphan Drug Regulations. Fed Regist [Internet]. 2013;78. Available from: <https://www.gpo.gov/fdsys/pkg/FR-2013-06-12/pdf/2013-13930.pdf>
33. European Medicines Agency. Orphan medicinal products - Major developments [Internet]. [cited 2018 Apr 23]. Available from: https://ec.europa.eu/health/human-use/orphan-medicines/developments_en
34. European Medicines Agency. Legal framework: Orphan Designation [Internet]. [cited 2018 May 3]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000552.jsp&mid=WC0b01ac058061ecb7
35. European Commission. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 [Internet]. 2006. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf
36. U.S. Food and Drug Administration. Orphan Drug Act [Internet]. 96 United States of America; 1983 p. 2049–66. Available from: <https://www.fda.gov/downloads/forindustry/developingproductsforrare diseasesconditions/howtoapplyfororphanproductdesignation/ucm517741.pdf>
37. U.S. Food and Drug Administration. The Orphan Drug Act (as amended) [Internet]. Available from: [http://old.iss.it/binary/cnmr4/cont/The Orphan Drug Act.1205943700.pdf](http://old.iss.it/binary/cnmr4/cont/The%20Orphan%20Drug%20Act.1205943700.pdf)
38. Food and Drug Administration (FDA). FDA at Rare Disease Day [Internet]. Developing Orphan Products: FDA and Rare Disease Day. 2011 [cited 2018 May 13]. Available from: <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm239698.htm>

39. U.S. Government. Electronic Code of Federal Regulations [Internet]. 2018 [cited 2017 Oct 21]. Available from: <https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=91b7be5e87481538e33a4c0a76ba7183&n=21y5.0.1.1.6&r=PART&ty=HTML>
40. U.S. Food and Drug Administration. Frequently Asked Questions on Patents and Exclusivity [Internet]. 2018 [cited 2018 May 3]. Available from: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm#howlongexclusivity>
41. Food and Drug Administration (FDA). Search Orphan Drug Designations and Approvals [Internet]. Developing Products for Rare Diseases & Conditions. 2018 [cited 2018 May 13]. Available from: <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>
42. European Medicines Agency. Authorisation of medicines [Internet]. What we do. [cited 2018 Apr 29]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47
43. European Medicines Agency. Procedure for orphan medicinal product designation [Internet]. Guidance for Sponsors United Kingdom; 2015 p. 1–12. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000268.jsp&mid=WC0b01ac058061f01c
44. European Medicines Agency. Post-orphan medicinal product designation procedures: Guidance for sponsors [Internet]. United Kingdom; 2015 p. 1–16. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196994.pdf
45. European Commission. Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products — state of play 2015 [Internet]. Brussels; 2016. Available from: https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_inv_cwd_20160126.pdf
46. European Medicines Agency. Orphan Medicines Figures [Internet]. 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC50018

5766.pdf

47. European Medicines Agency. Joint European Medicines Agency (EMA), US Food and Drug Administration (FDA), and Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) orphan medicinal product workshop [Internet]. Events. 2014 [cited 2018 May 4]. Available from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/12/event_detail_000810.jsp&mid=WC0b01ac058004d5c3
48. European Commission. What is Horizon 2020? [Internet]. [cited 2018 May 4]. Available from: <https://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020>
49. European Commission. Health, demographic change and well-being [Internet]. Horizon 2020. 2017. Available from:
http://ec.europa.eu/research/participants/data/ref/h2020/wp/2016_2017/main/h2020-wp1617-health_en.pdf
50. International Rare Diseases Research Consortium. History [Internet]. International Rare Diseases Research Consortium. [cited 2018 May 4]. Available from:
<http://www.irdirc.org/about-us/history/>
51. Lochmüller H, Farnell J, Le Cam Y, Jonker A, Lau L, Baynam G, et al. The International Rare Diseases Research Consortium: Policies and Guidelines to maximize impact. Eur J Hum Genet [Internet]. 2017;25:1293–302. Available from:
<http://dx.doi.org/10.1038/s41431-017-0008-z>
52. International Rare Diseases Research Consortium. Vision & Goals [Internet]. International Rare Diseases Research Consortium. [cited 2018 May 4]. Available from: <http://www.irdirc.org/about-us/vision-goals/>
53. International Rare Diseases Research Consortium. IRDiRC Recognized Resources [Internet]. 2018 [cited 2018 May 11]. Available from:
<http://www.irdirc.org/research/irdirc-recognized-resources/>
54. About Orphanet [Internet]. 2018 [cited 2018 May 12]. Available from:
https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN
55. United Nations. Universal Declaration of Human Rights [Internet]. [cited 2018 May 19]. Available from: <http://www.un.org/en/universal-declaration-human-rights/>

56. Rodriguez-Monguio R, Spargo T, Seoane-Vazquez E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? *Orphanet J Rare Dis* [Internet]. 2017;12(1):1–8. Available from: <http://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0551-7>
57. Ghooi RB. The Nuremberg Code—A critique. *Perspect Clin Res* [Internet]. 2011;2:72–6. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121268/?report=classic>
58. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. *Biomed Imaging Interv J* [Internet]. 2008;4(1):1–4. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097692/>
59. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [Internet]. 2018 [cited 2018 Jun 1]. Available from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
60. U.S. Department of Health & Human Services. The Belmont Report [Internet]. Ethical Principles and Guidelines for the Protection of Human Subjects of Research. 2016 [cited 2018 Jun 1]. Available from: <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html>
61. Vale M. Ética Da Investigação. Comissão Ética para a Investig Clínica [Internet]. 2009;(1):1–16. Available from: <http://www.ceic.pt/documents/20727/57508/Ética+da+Investigação/6b0bba31-029c-4d9a-b7ad-0e8a6dc2eebb%0Ahttp://www.ihmt.unl.pt/docs/Etica-da-Investigacao.pdf>
62. European Patients' Academy. Duties and rights of participants [Internet]. 2015 [cited 2018 Jun 9]. Available from: <https://www.eupati.eu/clinical-development-and-trials/participants-rights-responsibilities-organisations/>
63. Roche Farmacêutica. Direitos e deveres como participante num ensaio clínico [Internet]. 2018 [cited 2018 Jun 9]. Available from: <https://www.roche.pt/corporate/index.cfm/farmaceutica/ensaios-clinicos/participacao-num-ensaio-clinico/direitos-e-deveres/>
64. International Council for Harmonisation. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) [Internet]. 2016. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6

/E6_R2__Step_4_2016_1109.pdf

65. Global Genes. RARE Diseases: Facts and Statistics [Internet]. 2015 [cited 2018 Jun 10]. Available from: <https://globalgenes.org/rare-diseases-facts-statistics/>
66. INFARMED I.P. Lei da investigação clínica. Legis Farm Compil [Internet]. 2014; Available from: http://www.infarmed.pt/documents/15786/1068535/036-B1_Lei_21_2014_1alt.pdf
67. National Institutes of Health. Africa Clinical Studies Distribution [Internet]. clinicaltrials.gov. 2018 [cited 2018 Jun 13]. Available from: <https://clinicaltrials.gov/ct2/results/map?map=AF>
68. Weigmann K. The ethics of global clinical trials. EMBO Rep [Internet]. 2015;16(5):566–70. Available from: <https://onlinelibrary.wiley.com/doi/epdf/10.15252/embr.201540398>
69. U.S. National Library of Medicine. Learn About Clinical Studies [Internet]. 2017 [cited 2018 Jun 16]. Available from: <https://clinicaltrials.gov/ct2/about-studies/learn#WhatIs>
70. Mayfield Brain&Spine. Understanding clinical trials [Internet]. 2016 [cited 2018 Jun 16]. Available from: <https://www.mayfieldclinic.com/PE-ClinTrial.htm>
71. MStranlate. Understanding the Clinical Trial Process [Internet]. 2016 [cited 2018 Jun 23]. Available from: <http://www.mstranlate.com.au/understanding-clinical-trial-process/>
72. Australian Government. Phases of clinical trials [Internet]. Australian Clinical Trials. 2015 [cited 2018 Jun 17]. Available from: <https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials>
73. International Conference on Harmonization. ICH Harmonised Tripartite Guideline: General Considerations for Clinical Trials, E8. 1997;(July):1–13. Available from: <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/general-considerations-for-clinical-trials.html>
74. Mahan V. Clinical Trial Phases. Int J Clin Med. 2017;5(December):1374–83.
75. European Patients' Academy. Clinical trial designs [Internet]. Clinical Development and Trials. 2015 [cited 2018 Jun 17]. Available from: https://www.eupati.eu/clinical-development-and-trials/clinical-trial-designs/#Parallel_group_trial_design
76. Stang A. Randomized controlled trials-an indispensable part of clinical research.

- Dtsch Ärzteblatt Int [Internet]. 2011;108(39):661–2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196996/pdf/Dtsch_Arztebl_Int-108-0661.pdf
77. Suresh K. An overview of randomization techniques: An unbiased assessment of outcome in clinical research. J Hum Reprod Sci [Internet]. 2011;4(1):8–11. Available from: <http://www.jhrsonline.org/text.asp?2011/4/1/8/82352>
 78. Carranza J. Manual de Farmacia Clínica Y Atención Farmacéutica. Madrid: Elsevier; 2003.
 79. The Ohio State University. Site Monitor Visits [Internet]. Subject Management and Site Activities. 2018 [cited 2018 Jun 20]. Available from: <https://ccts.osu.edu/content/site-monitor-visits>
 80. Ogorka T, Chanchu G. Researchers Conduct NH Studies for Rare Diseases and Drug Development. Accelerating Res Dev [Internet]. 2017;1–4. Available from: <http://www.appliedclinicaltrialsonline.com/researchers-conduct-nh-studies-rare-diseases-and-drug-development>
 81. U.S. Food and Drug Administration. Rare Diseases: Common Issues in Drug Development [Internet]. FDA Guidance for Industry. 2015. Available from: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf>
 82. U.S. National Library of Medicine. International Collaborative Gaucher Group (ICGG) Gaucher Registry [Internet]. clinicaltrials.gov. 2017 [cited 2018 Jun 24]. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT00358943>
 83. Bishop P, Camblos L. Empowering CRAs in Rare Disease Studies. Appl Clin Trials [Internet]. 2017;20–2. Available from: <http://www.appliedclinicaltrialsonline.com/applied-clinical-trials-e-books-10-01-2017>
 84. Agency EM. Guideline on Clinical Trials in Small Populations [Internet]. 2006. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf
 85. Kaucic K, Plotkin H, Komelasky C. The Virtual Opportunity in Rare Diseases Trials. Appl Clin Trials [Internet]. 2017;10–4. Available from: <http://www.appliedclinicaltrialsonline.com/applied-clinical-trials-e-books-10-01-2017>

86. Carneiro AV. O exemplo da avaliação crítica de um ensaio clínico. J Port Gastrenterol [Internet]. 2008;15(2):30–6. Available from: <http://www.scielo.mec.pt/pdf/ge/v15n1/v15n1a07.pdf>
87. Berger VW, Alperson SY. A general Framework for the Evaluation of Clinical Trial Quality. Rev Recent Clin Trials [Internet]. 2009;4(2):79–88. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2694951&tool=pmcentrez&rendertype=abstract>
88. Sullivan EJ. Clinical Trial Endpoints [Internet]. FDA's Clinical Investigator Course. 2012. Available from: <https://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM337268.pdf>
89. Hughes DA. Pharmacoeconomics. Br J Clin Pharmacol [Internet]. 2012;73(6):968–72. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3391529/pdf/bcp0073-0968.pdf>
90. Evaluate Pharma. Orphan Drug Report 2018 [Internet]. 2018. Available from: <http://info.evaluategroup.com/rs/607-YGS-364/images/OD18.pdf>
91. Drummond MF. Challenges in the economic evaluation of orphan drugs. Eurohealth (Lond) [Internet]. 2008;14(2):16–7. Available from: <http://apps.who.int/medicinedocs/documents/s20976en/s20976en.pdf>
92. Hyry H, Stern A, Cox T, Roos J. Limits on use of health economic assessments for rare diseases. Q J Med [Internet]. 2014;107:241–5. Available from: <https://academic.oup.com/qjmed/article/107/3/241/1570371>
93. INFARMED I.P. Perguntas frequentes [Internet]. Sobre o INFARMED I.P. 2018. Available from: <http://www.infarmed.pt/web/infarmed/perguntas-frequentes-area-transversal/sobre-o-infarmed>
94. Diniz A, Coelho A, Pereira C. Cartão da Pessoa com Doença Rara 2017 [Internet]. 2018 [cited 2018 Jun 30]. p. 5–6. Available from: <https://www.dgs.pt/paginas-de-sistema/saude-de-a-a-z/cartao-da-pessoa-com-doenca-rara.aspx>
95. INFARMED I.P. Investimento de 90 milhões de euros em 2017. In: Mais de 60 medicamentos utilizados no tratamento de doenças raras. 2018.
96. Infarmed I.P. Meio hospitalar - Monitorização do consumo de medicamentos [Internet]. 2018. Available from:

<http://www.infarmed.pt/documents/15786/2682984/abril/ecf0aabd-d152-4c5c-94f0-045429478615?version=1.0/241/1570371>

9. Annexes

Annex I – Excerpt of the Electronic Code of Federal Regulations, Title 21, Part 316, Content and format of a request for orphan-drug designation, FDA:

“(a) A sponsor that submits a request for orphan-drug designation of a drug for a specified rare disease or condition shall submit each request in the form and containing the information required in paragraph (b) of this section. A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new use for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. More than one sponsor may receive orphan-drug designation of the same drug for the same rare disease or condition, but each sponsor seeking orphan-drug designation must file a complete request for designation as provided in paragraph (b) of this section.

(b) A sponsor shall submit two copies of a completed, dated, and signed request for designation that contains the following:

(1) A statement that the sponsor requests orphan-drug designation for a rare disease or condition, which shall be identified with specificity.

(2) The name and address of the sponsor; the name of the sponsor's primary contact person and/or resident agent including title, address, telephone number, and email address; the generic and trade name, if any, of the drug, or, if neither is available, the chemical name or a meaningful descriptive name of the drug; and the name and address of the source of the drug if it is not manufactured by the sponsor.

(3) 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.

(4) A description of the drug, to include the identity of the active moiety if it is a drug composed of small molecules, or of the principal molecular structural features if it is composed of macromolecules; its physical and chemical properties, if these characteristics can be determined; and a discussion of the scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition, including all relevant data from in vitro laboratory studies, preclinical efficacy studies conducted in an animal model for the human disease or condition, and clinical experience with the drug in the rare disease or condition that are available to the sponsor, whether positive, negative, or inconclusive. Animal toxicology studies are generally not relevant to a request for orphan-drug designation. Copies of pertinent unpublished and published papers are also required.

(5) Where the sponsor of a drug that is otherwise the same drug as an already approved drug seeks orphan-drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug.

(6) Where a sponsor requests orphan-drug designation for a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people (“orphan subset”), a demonstration that, due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for use of the drug.

(7) A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries, e.g., IND and marketing application status and dispositions, what uses are under investigation and in what countries; for what indication is the drug approved in foreign countries; what adverse regulatory actions have been taken against the drug in any country.

(8) Documentation, with appended authoritative references, to demonstrate that:

(i) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in §316.21(b), or

(ii) For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in §316.21(c).

(c) Any of the information previously provided by the sponsor to FDA under subpart B of this part may be referenced by specific page or location if it duplicates information required elsewhere in this section.”

Annex II – Excerpt of the guidance “Procedure for orphan medicinal product designation” with documents needed for the submission of an orphan medicinal product designation application, EMA:

Document	Format
Cover letter	signed PDF
EMA application form or Common EMA/FDA application form The application should be signed by no other than the sponsor. If the sponsor does not have the Unique Product Identifier (UPI) to complete the form the EMA will allocate one on receipt of the application.	e-signed PDF ²
Scientific sections A-E of the application	Word (97-2003)
Proof of establishment of the sponsor in the EU. The sponsor should have a permanent physical address in the EU and provide full details in the application form including the name of a contact person at the sponsor premises able to receive any documents in person.	PDF
If applicable, letter of authorisation from the sponsor for the person/company acting on their behalf during the procedure	signed PDF
Translations of the name of the product and the proposed orphan indication into the official languages of the European Union, plus Icelandic and Norwegian	Word
Bibliography saved as single publications and titled as first author and year, such as in 'Smith PH et al 2004.PDF'	PDF

Annex III – Excerpt of a Practical Example of an Orphan Medicinal Product Designation
Submitted to EMA: “Public summary opinion on orphan designation – Alpha-galactosidase A for the treatment of Fabry disease”, EMA



17 November 2011
EMA/COMP/235368/2008 Rev.1
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Alpha-galactosidase A for the treatment of Fabry disease

Please note that this product was withdrawn from the Community Register of designated orphan medicinal products in August 2011 at the end of the period of market exclusivity.

On 8 August 2000, orphan designation (EU/3/00/002) was granted by the European Commission to TKT Europe-SS AB, Sweden, for alpha-galactosidase A for the treatment of Fabry disease.

The sponsor applied for a change of name to Shire Human Genetic Therapies AB in September 2010.

What is Fabry disease?

Fabry disease comprises a group of inherited lysosomal storage disorders. Lysosomes are small vesicles within cells containing enzymes that are able to destroy or transform different substances of the cell, such as proteins, fat, nucleic acids (components of the genetic material) and sugars. Any change of the lysosomal enzymes causes abnormal accumulation of the substance (also known as substrate) normally transformed by it. Cells are unable to destroy or eliminate accumulated substrates, and high levels of them can be toxic leading to damage and malfunction of the organ where accumulation occurs. In Fabry disease, the activity of the lysosomal enzyme alpha-galactosidase A is impaired or absent. Fabry disease is a heterogenous disorder with variable onset of symptoms that affect several organs. Glycosphingolipids (biological molecules composed of a type of sugar and lipid) is the substrate that accumulates in Fabry disease, and severity of the disease depends on the level of accumulation. Fabry disease affects the nervous system, kidneys, heart, skin and gastrointestinal system. Some of the most common pathological symptoms are skin lesions and burning pain of the extremities. Fabry disease is chronically debilitating and life threatening.

What is the estimated number of patients affected by the condition?

At the time of designation, Fabry disease affected approximately 0.013-0.027 in 10,000 people in the European Union (EU)*. This is equivalent to a total of 500-1,000 people, and is below the threshold for

* Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union. This represents a population of 377,000,000 (Eurostat 2001).



orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of submission of application for orphan drug designation, there were no satisfactory methods authorised for the treatment of Fabry disease. Some patients with advanced renal failure due to the disease could be treated with dialysis and/or renal transplantation and treatments for specific symptoms, such as convulsions, were used.

How is this medicine expected to work?

The product works as an enzyme replacement therapy. It is expected to replace the missing or defective alpha-galactosidase in patients with Fabry disease, reducing the accumulation of glycosphingolipids. This is expected to relieve the symptoms.

What is the stage of development of this medicine?

The effects of alpha-galactosidase A were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with Fabry disease were ongoing.

Alpha-galactosidase A was not authorised anywhere worldwide for the treatment of Fabry disease, at the time of submission. Orphan designation of alpha-galactosidase A was granted in the United States for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 11 July 2000 recommending the granting of this designation.

Update: Alpha-galactosidase A (Replagal) was authorised in the EU on 4 May 2001 for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α -galactosidase A deficiency).

More information on Replagal can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find_medicine/Human_medicines/European_Public_Assessment_Reports

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Shire Human Genetic Therapies AB
Rinkebyvägen 11B
SE 182 36
Danderyd
Sweden
Telephone: +46 8 5449 6400
Telefax: +46 8 5449 6429

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- [Orphanet](#), a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
- [European Organisation for Rare Diseases \(EURORDIS\)](#), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.