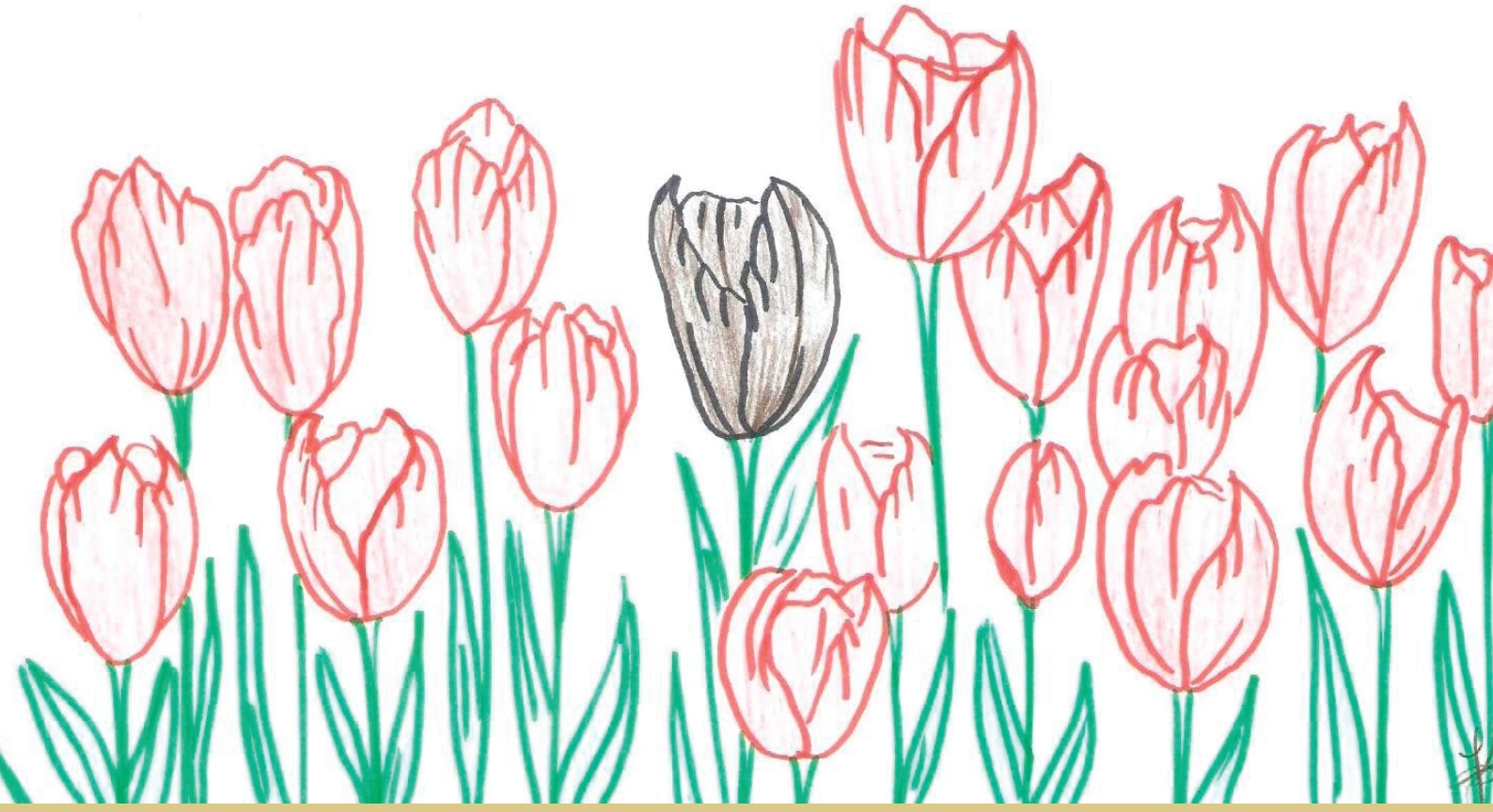

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REGULATORY AND ETHICAL ISSUES FOR ORPHAN MEDICINES

Dissertação de Mestrado em Tecnologias do Medicamento, orientada pelo Professor Doutor João José Sousa e pela Professora Doutora Maria Eugénia Pina e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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Universidade de Coimbra

Regulatory and Ethical Issues for Orphan Medicines

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Mestrado em Tecnologias do Medicamento

Prof. Doutor João José Sousa

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When it is obvious that the goals cannot be reached,

don´t adjust the goals, adjust the action steps

Confucius

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Obrigada!

Contents

Acronyms

ADNI – Alzheimer's Disease Neuroimaging Initiative

ATC - Anatomical Therapeutic Chemical code

BLA – Biologics License Application

BPCA – Best Pharmaceuticals Children Act

CAVOMP – Clinical Added Value of Orphan Medicinal Products

CDER – Center for Drug Evaluation and Research

CFFT – Cystic Fibrosis Foundation Therapeutics

CHMP - Committee for Medicinal Products for Human Use at EMA

COMP - Committee on Orphan Medicinal Products at EMA

DALY – Disability-adjusted life years

EC - European Commission

ECEGRD – European Commission Expert Group on Rare Diseases

ECRD - European Conference on Rare Diseases

EGAN – Patients Network for Medical Research and Health

EMA - European Medicines Agency

EPPOSI – European Platform for Patient's Organizations, Science and Industry

EU - European Union

EUCERD - European Union Committee of Experts on Rare Diseases

EURORDIS - European Organization for Rare Diseases

FDA - Food and Drug Administration

FDAMA – Food and Drug Administration Modernization Act

GENCODYS – Genetic and Epigenetic Networks in Cognitive Dysfunction

GRIP – Global Research in Pediatrics

HTA – Health Technology Assessment

ICD – International Classification of Diseases

ICH – International Council for Harmonization

ICORD – International Conferences on Rare Diseases and Orphan Drugs

IND - Investigational New Drug

INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

MA - Market Authorization

MED – Minimum Effective Dose

MS - Member State

MTD – Maximum Tolerable Dose

NCATS – National Center for Advancing Translational Sciences

NDA – New Drug Application

NHS - National Health System

NICE – National Institute for Health and Care Excellence

NIH – National Institutes of Health

NORD – National Organization for Rare Disorders

NTD – Neglected Tropical Disease

ODA – Orphan Drug Act

ODD – Orphan Drug Designation

OOPD – Office of Orphan Products Development

PA – Protocol Assistance

PAHO – Pan American Health Organization

PDUFA – Prescription Drug User Fee Act

PIP – Paediatric Investigation Plan

PLA – Product License Application

PREA – Pediatric Research Equity Act

PRV – Priority Review Voucher

PUMA – Paediatric Use Marketing Authorization

RDCRN – Rare Diseases Clinical Research Network

RDTF - EC Rare Disease Task Force

REMS – Risk Evaluation and Mitigation Strategy

SA – Scientific Advice

SAWP – Scientific Advice Working Party

SMEs – Small and Medium-sized Enterprises

WG - Working Group

WHO - World Health Organization

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Resumo

Os medicamentos órfãos são medicamentos utilizados no diagnóstico, prevenção ou tratamento de doenças raras debilitantes ou que coloquem a vida em risco. Designam-se de 'órfãos' porque a indústria farmacêutica tem pouco interesse, sob normais condições de mercado, em desenvolver e comercializar fármacos dirigidos para apenas um pequeno número de doentes que sofrem de condições patológicas raras (EURORDIS, 2005).As doenças raras são frequentemente crónicas, progressivas, degenerativas, debilitantes e, muitas vezes, colocam a vida em risco. Existem, aproximadamente, entre 6 000 a 8 000 doenças raras; à volta de 75% afetam crianças e 30% destes doentes morrem antes dos 5 anos de idade. Cerca de 80% das doenças raras têm origem genética identificada. Um dos principais problemas destas patologias é que sintomas relativamente comuns podem esconder-se no quadro clínico que os portadores de doenças raras apresentam, conduzindo frequentemente a diagnósticos errados e, consequentemente, a um atraso no diagnóstico final e correto (EURORDIS, 2005; Berman, 2014).

A legislação respeitante a medicamentos órfãos na Europa chegou em 2000 (European Commission, 2000). O objetivo é proporcionar aos doentes portadores de doenças raras o acesso a tratamentos de elevada qualidade através do estímulo à investigação e desenvolvimento de medicamentos para estas patologias. A legislação fornece incentivos à indústria farmacêutica no desenvolvimento de medicamentos órfãos (EURORDIS, 2005; Berman, 2014). Também nos Estados Unidos da América (EUA), um documento aprovado em 1983 – *Orphan Drug Act* – fornece incentivos ao desenvolvimento de produtos órfãos para o tratamento de doenças raras (Meyers, 2000).

Apesar do progresso no campo das doenças raras, continua a existir necessidade de investimento nas doenças tropicas negligenciadas cujo *pipeline* é limitado (Wizemann, Robinson and Giffin, 2009). Um dos pontos mais interessantes relacionados com os medicamentos órfãos é a oportunidade comercial que estes representam atualmente.

Palavras-chave: medicamentos órfãos, doenças raras, doenças negligenciadas, assuntos regulamentares; aspetos éticos

Abstract

Orphan medicines are medicinal products intended for diagnosis, prevention or treatment of life-threatening or debilitating rare diseases. They are 'orphans' because the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare conditions (EURORDIS, 2005).Rare diseases are often chronic, progressive, degenerative, disabling and often life-threatening. There are between 6,000 and 8,000 rare diseases: 75% affect children and 30% of these patients die before the age of 5 years. It´s important to know that 80% of rare diseases have identified genetic origins (EURORDIS, 2007; European Commission, 2013). One of the biggest problems is that relatively common symptoms can hide underlying rare diseases, leading to misdiagnosis and delay in final and correct diagnosis (EURORDIS, 2005; Berman, 2014).

Orphan legislation in Europe came into force in 2000 (European Commission, 2000). Its aim is to give patients suffering from rare diseases access the highest quality of treatments by stimulating research and development of medicines for their conditions. The legislation provides a set of incentives to the pharmaceutical industry to develop orphan medicines (EURORDIS, 2005; Berman, 2014). Also in the United States of America, (USA) the Orphan Drug Act, since 1983, provides incentives for pharmaceutical manufacturers to develop orphan products for the treatment of rare diseases and conditions (Meyers, 2000).

Despite the progress in the field of rare diseases, there is still a need of investment in neglected tropical diseases which pipeline is very limited (Wizemann, Robinson and Giffin, 2009). Nowadays, one of the most interesting points of orphan medicines is related to the commercial opportunity.

Keywords: rare diseases, orphan medicines, neglected diseases, regulatory affairs, ethical aspects

Introduction

Rare diseases are sometimes referred to as 'orphan diseases'. The term is apt for several reasons. First, the term 'orphan' applies to children, and it happens that neonates, infants and children are at highest risk for the most devastating rare diseases. Second, the concept of an 'orphan disease' implies a lack of stewardship. For far too long, rare diseases were neglected by clinicians, medical researchers, the pharmaceutical industry, and society in general. Rare diseases manifest as strange and often disfiguring disorders that occur without any obvious cause. Rare diseases are easily misdiagnosed, and are often mistaken for a common disease or for some other rare disease. Obviously, it's impossible for any physician to attain clinical experience with more than a small fraction of the total number of rare diseases (Sharma *et al.*, 2010; Berman, 2014).

Excluding genes causing rare cancers, more than 2000 genes have been linked to 2000 rare diseases. In most cases, these links are presumed to be causal. Progress in genetic diseases greatly accelerated in the 1960s, and the earliest advances came to the group of diseases known as inborn errors of metabolism (Berman, 2014).

Rare diseases, taken together, aren't rare at all. According to the National Institutes of Health, 25-30 million Americans have one of the nearly 7,000 diseases that are officially deemed 'rare' (NIH, 2013). Similar to the United States, Europe has approximately 30 million people living with rare diseases (European Commission, 2013).

Patients with a rare disease have an equal right to medicines as do other patients with a well-known disease. In this context, orphan drugs are a special class of medicines because they would not be developed and marketed if there were no incentives and specific orphan drug legislation to promote their research and development. Thus, orphan diseases require some attention from governments and competent regulatory authorities. In fact, several governments developed specific legislation and policies, which stimulate research and development of orphan drugs for specific diseases (Franco, 2013).

Presentation of the Project and Goals

The regulatory and economic incentives for industry to develop drugs for rare diseases previously introduced in the United States in 1983, and later in Europe, have resulted in substantial improvements in the treatment for patients with a range of rare diseases. However, the advent of orphan drug development has also triggered several questions, from the definition of rarity to the pricing of orphan drugs and their impact on health-care systems.

Main Objective:

Describe a regulatory framework of orphan medicines in USA and UE, including specific legislation and guidelines, orphan medicine designation process, economic incentives and impact of these in market approval.

Specific Objectives:

- Present an overview of rare diseases, including causes and examples;
- Realize the evolution of legislation in the framework of orphan medicines;
- Identify the key documents in orphan legislation in USA and EU;
- Emphasize the role of patient organizations in orphan legislation process;
- Compare the orphan medicine definition in USA and EU, the orphan designation process as well as their intervenients and economic incentives in these two geographic areas;
- Understand the current model for financing drug development and ways to facilitate drug development, especially alternative funding models;
- Identify difficulties and obstacles in the clinical development of orphan drugs and present regulatory strategies and alternative clinical trial designs that facilitate their development;
- Provide a brief ethical reflection on research funding of orphan medicines as well as challenges, progress and opportunities in neglected tropical diseases;
- Discuss the pharmacoeconomic analysis and what has changed in terms of commercial opportunity after the introduction of orphan drug legislation.

Chapter 1: Orphan Diseases

The term "orphan disease" came from the Greek word *orphanos*, which means a child who has lost one or both parents or an adult who has lost a child (Hernberg-Sthal and Reljanovic, 2013). An orphan disease is an illness that has not been addressed by the pharmaceutical industry because it provides little financial incentive for the private sector to develop and market new medicinal products to diagnose, prevent or treat it. Orphan diseases include, as I will explain in more detail in the following chapters, **rare diseases** and **neglected tropical diseases**.

1.1 Rare Diseases

There's no universal definition for rare diseases (Richter *et al.*, 2015). In Europe, according to Regulation (EC) N°141/2000 of the European Parliament and of Council of 16 December 1999 on orphan medicinal products (European Commission, 2000), rare diseases are illnesses that affect less than 5 in 10,000 citizens in Europe.

There are between 6,000 and 8,000 rare diseases: 75% affect children and 30% of these patients die before the age of 5 years (EURORDIS, 2005). However, rare diseases can afflict anyone, at any age (Field and Boat, 2010).

Some conditions are extremely rare, found in only a few or a few dozen people (Field and Boat, 2010). A disease can be rare in one region, but common in another. This is the case of Beta Thalassemia, caused by a mutation in the HBB gene, which is rare in US, but is particularly prevalent in the Mediterranean, Middle East, Africa, central Asia, the Indian subcontinent, and the Far East (NORD, 2015). There are also many common diseases, like cancer, whose variants are rare (Berman, 2014).

In the European Union rare diseases may affect 30 million citizens (EURORDIS, 2005): these patients are particularly isolated and vulnerable.

The lack of specific health policies for rare diseases and the scarcity of experts, translate into delayed diagnosis and difficult access to care. This results in additional physical, physiological and intellectual impairments, inadequate or even harmful treatments and loss of confidence in the health care system. Misdiagnosis and non-diagnosis are the main hurdles to improving quality of life for thousands of rare disease patients (Berman, 2014; Rodwell and Aymé, 2014). Particularly when a condition is extremely rare, patients and families often have to travel long

distances to consult with the few experts who have experience in treating and studying their rare diseases (Field and Boat, 2010).

Most rare diseases are genetic diseases, rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases (Berman, 2014).

1.1.1. Causes and Examples of Rare Diseases

In the past two decades, epidemiologic, molecular, and other research that takes advantage of scientific and technological advances in the biological sciences has greatly increased the number of rare diseases that have an identified cause – usually, although not invariably, genetic. Knowing the genetic, infectious, or other cause of a disease does not necessarily mean that researchers understand the mechanism of the disease. Nonetheless, identifying the cause of a condition is usually an important step in building the knowledge base for prevention or effective treatment. Some rare conditions have multiple possible types of causes. For certain rare diseases that have been named and characterized for decades, investigators still have not determined the cause (Field and Boat, 2010).

1.1.1.1. Genetic Causes

The European Organization for Rare Diseases (EURORDIS) estimates that there are approximately 6,000-8,000 rare diseases. Within these, about 80% or more are caused by genetic changes, further strengthening the relations between genotypes and phenotypes associated with these particular conditions (EURORDIS, 2005; Field and Boat, 2010). Many if not most are caused by defects in a single gene (e.g. Friedreich's ataxia). Multiple different mutations in that single gene may result in disease of varying features or severity. Other diseases have several named variants, each caused by a defect in a different gene (e.g. Fanconi anemia). In some rare conditions, multiple genes may contribute collectively to manifestations of the disorder (Ameziane *et al.*, 2015).

Rare genetic conditions are often inherited but may also arise as a result of sporadic or chance mutations (e.g. Marfan syndrome). Some diseases such as sarcoidosis are known or suspected to be heritable, but the specific genetic mutation or mutations have not yet been identified. For other diseases, known genetic causes do not explain all cases and other genes are suspected to play a role (Field and Boat, 2010).

The Table 1 contains only a few examples of rare genetic diseases.

Table 1 - Unusual Genetic Mutations in Humans

Disease	Cause	Characteristics
Hutchinson-Gilford Progeria Syndrome (P<1/1 000 000)	Mutation in the LMNA gene. The most common mutation is located at codon 608 (G608G) (Pollex and Hegele, 2004).	Rare, fatal, autosomal dominant and premature aging disease. Growth reduction, failure to thrive, typical facial appearance (prominent forehead, protuberant eyes, thin nose with a beaked tip, thin lips, protruding ears) (Pollex and Hegele, 2004; Faivre-Olivier, 2014).
Cystic fibrosis (P: 1-9/100 000)	Caucasians (70%): Three base pairs in exon 10 of the gene located ate 7q31-32 in 7th chromosome are deleted (F508del;stop codon) (Hernberg-Sthal and Reljanovic, 2013; Matteis, De *et al.*, 2016).	Mucus becomes thick and sticky, which blocks airways and provides a substrate for bacterial growth in the lungs, leading recurrent infections. Progressive breathing difficult is typical. Life expectancy is generally reduced (Hernberg-Sthal and Reljanovic, 2013; Matteis, De *et al.*, 2016).
Friedreich's ataxia (P: 1-9/100 000)	X25 (FXN) gene in chromosome 9(Hernberg-Sthal and Reljanovic, 2013) The length of the GAA triplet repeats in the first intron of the FXN gene is an important factor in the pathogenesis (Richardson *et al.*, 2013).	Uncoordinated movements, gait disorder, slurred speech, muscle weakness or paresis mainly of legs (Hernberg-Sthal and Reljanovic, 2013; Richardson *et al.*, 2013).
Huntington's disease (P: 5-10/100 000)	Expansion of nucleotide triplet repeats (CAG coding for glutamine) in the Huntington gene on the short arm of chromosome 4 (4p16.3) (Hernberg-Sthal and Reljanovic, 2013; Thomas, 2015).	Unwanted choreatic (involuntary jerky) movements, muscle rigidity and cognitive decline (dementia) (Hernberg-Sthal and Reljanovic, 2013; Thomas, 2015).
Pompe's disease (P: 1/138 000)	Various mutations in chromosome 17q23; most frequently a point mutation in a splice site: the acid maltase, which converts glycogen into glucose, is deficient (Ploeg and Reuser, 2008; Hernberg-Sthal and Reljanovic, 2013).	Hypotonia, swallowing difficulties, hypertrophic cardiomyopathy and hepatomegaly (Ploeg and Reuser, 2008; Hernberg-Sthal and Reljanovic, 2013).
Gaucher disease (P: 1-100 000)	Lysosomal storage disease. Glucosylceramidase is deficient (1q21) (Hernberg-Sthal and Reljanovic, 2013; Moraitou *et al.*, 2014).	Bone marrow depression, bruising, fatigue, anaemia, osteoporosis, yellowish skin and scleral deposits, enlargement of the liver and spleen (Hernberg-Sthal and Reljanovic, 2013).

*P: prevalence

1.1.1.2. Rare Cancers

There are more than 3000 named types of cancer, and many of these cancers have well-defined subtypes, with their own morphologic, clinical or genetic characteristics. Including defined subtypes, there are well over 6000 rare types of cancer (Berman, 2014). Regarding the burden of rare tumors, there is still no generally accepted definition to measure it. The Surveillance of Rare Cancers in Europe project (funded by the European Commission) aimed at providing a definition of "rare cancer", a list of cancers and rare cancer burden indicators, based on population-based cancer registry data, across Europe. An international consensus group agreed that incidence is the most appropriate indicator for measuring rare cancers frequency and set the threshold for rarity at 6/100,000/year (Gatta *et al.*, 2010).

Two projects have been funded by the EC concerning rare cancers: RareCare (2007-2010) and RareCareNet (starting on 1 May 2012) (Rodwell and Aymé, 2014).

The Table 2 contains three examples of rare cancers:

Table 2 - Examples of rare cancers

Disease	Cause	Characteristics
Hairly cell leukaemia (HCL) **(P: 1/500 000)**	Recurrent somatic mutations have been detected (BRAF V600E) (Tiacci *et al.*, 2011).	Indolent course, marked splenomegaly, frequent progressive pancytopenia, rare circulating tumor cells, and usually no lymphadenopathy (Tiacci *et al.*, 2011; Hernberg-Sthal and Reljanovic, 2013). Bone marrow, spleen and liver are infiltrated by leukemic B cells showing abundant cytoplasm with "hairy" projections and unique immunophenotypic features (Tiacci *et al.*, 2011).
ALK-positive non-small cell lung cancer **(I: Unknown)**	EML4-ALK fusion oncogene: expression of a chimeric tyrosine kinase of echinoderm microtubule-associated protein-like 4 (EML4) fused to the kinase domain of the anaplastic lymphoma kinase (ALK) (Hernberg-Sthal and Reljanovic, 2013; Chiari *et al.*, 2015; Iacono *et al.*, 2015).	Most ALK+ patients have advanced disease at time of diagnosis, which may reflect the aggressiveness of these tumors and their predilection for cerebral and hepatic metastases in addition to pleural and pericardial effusions (Chia *et al.*, 2014).

Disease	Cause	Characteristics
Pseudomyxoma peritonei **(I: 1/1000 000/year)**	K-Ras (p53) gene is probably involved.	Diffusely spread collection of gelatinous material into the intra-abdominal cavity along with scattered mucinous implants over peritoneal surfaces and omentum with variable cellularity (Emam, Ghanim and Ghanim, 2015). Abdominal distension, weight changes, constipation, vomiting and dyspnea (Hernberg-Sthal and Reljanovic, 2013).

*I:Incidence

1.1.1.3. Auto-immune diseases

Autoimmune diseases can affect almost any part of the body: heart, brain, nerves, muscles, skin, lungs, glands, the digestive tract and blood vessels. Many autoimmune diseases do not restrict themselves to one part of the body. The classic sign of an autoimmune disease is inflammation, which can cause redness, heat, pain and swelling (NIH, 2012). Examples of such diseases are shown in Table 3:

Table 3 - Examples of autoimmune disorders.

Disease	Cause	Characteristics
Schmidt's Syndrome (Type II polyglandular autoimmune syndrome) **P: Unknown**	Humoral and cell-mediated immune mechanisms against adrenal cortex associated with autoimmune destruction of other endocrine glands.	Primary adrenal insufficiency (Addison's disease), type I diabetes and autoimmune thyroiditis (Gupta and Nagri, 2012).
Balo's concentric sclerosis **P: Unknown**	Rare variant of Multiple Sclerosis; the cause is not known.	Acute onset and steady progression to major disability within a few months (Aghaghazvini *et al.*, 2013).
Ormond's disease (Retroperitoneal fibrosis) **P: 1-9/100 000**	Extra fibrous tissue forms in the area behind the stomach and intestines. The tissue forms a mass that can cause ureteral obstruction.	Severe abdominal pain, nausea and vomiting, kidney failure and anuria (Aziz, Conjeevaram and Phan, 2006).

1.1.1.4. Congenital malformations

Congenital malformations, also known as congenital diseases or birth defects, are conditions existing at or before birth. These includes errors of morphogenesis, infections, epigenetics modifications or chromosomal abnormality. For example, *acalvaria*, it's a rare congenital malformation characterized by an absence of flat bones of skull, *dura mater*, and associated muscles in the presence of normal cranial contents and facial bones (Gupta and Kumar, 2012).

1.1.1.5. Infectious Agents

Regarding rare infectious diseases, well over 1400 different infectious organisms have been reported in the literature. A single infectious organism may manifest as several different named conditions, each with its own distinctive clinical features (Berman, 2014). Despite their rarity, some infectious such as rabies, botulism and Rocky Mountain spotted fever are relatively well publicized and feared. Some infectious are thought to be rare worldwide. Others, however, are rare in wealthy countries but common in less economically developed countries (see 1.2. Neglected Tropical Diseases). Research suggests that genetic factors may affect susceptibility to infectious agents, either increasing susceptibility or having a protective effect. For example, research indicates that sickle cell trait contributes to resistance against malaria. Other genes are likely to affect susceptibility to malaria and leprosy (Field and Boat, 2010).

1.1.1.6. Toxic Agents

Some rare diseases or conditions result from exposure to natural or manufactured toxic substances, including substances that appear as product contaminants. Examples include arsenic and mercury poisoning, mesothelium (cancer caused by exposure to asbestos) and eosinophilia-myalgia syndrome, which is associated with contaminated tryptophan (Berman, 2014).

1.1.2. Epidemiology of Rare Diseases

Defining and counting rare diseases is not straightforward. Difficulties in obtaining definitive diagnoses contribute, as limitation to the systems for reporting and tracking such diagnoses. In addition, countries have adopted different definitions of a rare disease. Therefore, the epidemiology of rare diseases, including the determination of prevalence, incidence and

patterns of disease is inexact. If effective but not curative treatment can turn a rare disease into a common one, effective preventive can, conversely, turn a common condition into a rare disease. This is the case with many once common childhood infections such as mumps and measles. However, development of drug-resistant infectious agents and the opposition of some parents to childhood vaccinations could reverse the situation for some now rare diseases (Field and Boat, 2010).

The objectives of epidemiologic research in rare diseases include determining the extent, distribution and burden of these diseases at the population level and helping identify factors that may cause or contribute to their development. Basic epidemiologic studies generate estimates of incidence and prevalence. Epidemiological data have a variety of policy uses, including providing the prevalence data to support an "orphan" designation. Companies seeking this designation must provide the documentation that the proposed indication or use for the drug involves fewer than 200,000 people in the United States and fewer than 5 in 10,000 in Europe (Field and Boat, 2010).

Natural history studies are another pillar of epidemiologic research on rare conditions; these studies track the course of a disease over time, identifying demographic, genetic, environmental and other variables that correlate with its development and outcomes in the absence of treatment; The referred investigation studies also generate important information about clinical (phenotypic) variation and have helped to identify subtypes of rare disorders that may be produced by different genes or by epigenetic factors that influence the effects of a gene. Such longitudinal studies are often a high priority for a rare disease organization (Field and Boat, 2010).

Data for prevalence or incidence calculations may come from birth certificates or death certificates; hospital discharge, insurance claims, and other administrative databases; patient registries; special surveillance studies; and newborn and other screening programs (Field and Boat, 2010; Orphanet, 2015).

One difficulty confronting epidemiologic studies involves the lack of condition-specific codes in the World Health Organization's (WHO) International Classification of Diseases (ICD). The ICD provides the international standard diagnostic classification that is used for epidemiologic studies as well as for key health system management functions. Much of the preparatory work on rare disease coding has been conducted by Orphanet, a European

information consortium which is also the source of the prevalence data (Field and Boat, 2010; Orphanet, 2015).

1.1.2.1. Prevalence Data on Rare Diseases

The prevalence of a disease in an area or jurisdiction may be expressed as the number, percentage, or a proportion of people alive on a certain day who have been diagnosed with the disease. The European Union defines a rare disease as one with a prevalence of no more than 5 people per 10,000 population, whereas the United States sets a numerical maximum of fewer than 200,000 people (Field and Boat, 2010; Richter *et al.*, 2015).

Prevalence is a function of both the incidence of disease (number of new cases reported in a given period) and the survival (duration of illness for self-limiting or curable diseases such as many infections) (Field and Boat, 2010; Orphanet, 2015).

A report from Orphanet lists estimated European prevalence for almost 2,000 rare diseases. The list has much in common with the National Institutes of Health (NIH) list of rare conditions. The demography, living conditions, and other characteristics of Europe and the United States likewise have much in common. In general, the limitations of the data in the Orphanet report include the use of single numbers for conditions with widely varying estimates of prevalence in the literature and the lack of bibliographic citations and explanatory details. Figure 1 and Figure 2 show the distribution of rare conditions according the prevalence as presented in the Orphanet report (Field and Boat, 2010).

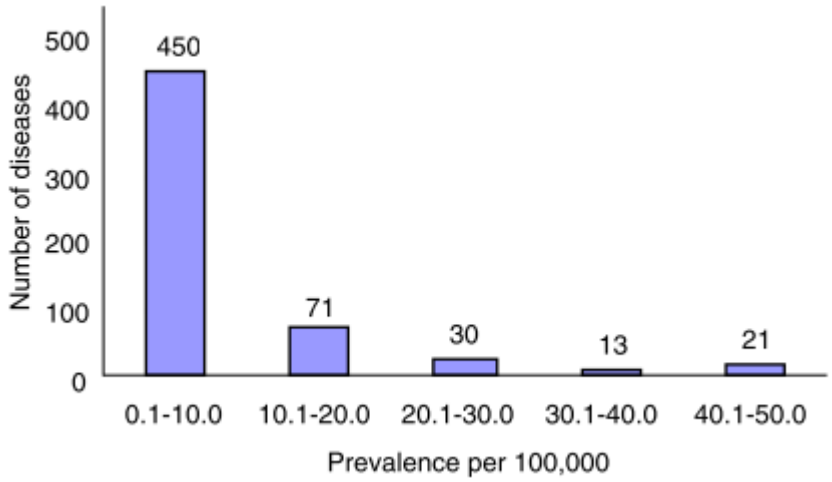


Figure 1 - Number of rare diseases by prevalence up to 50/100,000 (Field and Boat, 2010).

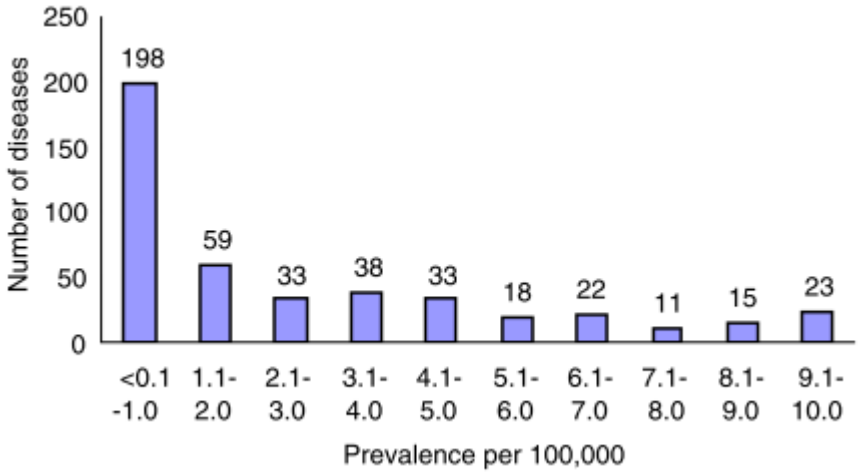


Figure 2 - Number of rare diseases by prevalence of 10/100,000 or less (Field and Boat, 2010).

1.2. Neglected Tropical Diseases (NTDs): overview

Neglected tropical diseases are common communicable diseases that mainly affect patients living in developing countries. They are not a public health priority in the industrialized countries, thus, little research and drug development are performed for these diseases. They are neglected by the pharmaceutical industry because the market is usually seen as unprofitable. There is a need for economic regulation and alternative approaches in this field in order to create incentives aimed at stimulating research and development of treatments; neglected diseases are therefore not rare diseases (EURORDIS, 2005; Field and Boat, 2010; Hotez, 2013).

The following table shows a list of 17 neglected tropical diseases that has been expanded by WHO since 2005 (see Table 4).

Table 4 - Neglected Tropical Diseases. Adapted from (Hotez, 2013).

Infection type	Disease or pathogen name
Helminth (worm infections)	
Soil-transmitted helminth infections	Ascariasis (roundworm infection) Hookworm infection Trichuriasis (whipworm infection)
Other helminth infections	Schistosomiasis (snail fever) Lymphatic filariasis (elephantiasis)

Infection type	Disease or pathogen name
Other helminth infections (cont.)	Onchocerciasis (river blindness) Food-borne trematode infections (liver fluke, lung fluke, intestinal fluke) Cysticercosis Human echinococcosis (hydatid cyst) Dracunculiasis (guinea worm infection)
Protozoan infections	Leishmaniasis Chagas disease Human African trypanosomiasis (sleeping sickness)
Bacterial infections	Trachoma Buruli ulcer Leprosy Yaws and endemic treponematoses
Viral infections	Dengue Rabies

Zika virus become an important news item during 2016 year. Zika virus infection is an arbovirus infection transmitted by several different species of *Aedes* mosquitoes. Like many flaviviruses including dengue virus, zika virus typically causes fever, rash, headaches, and arthralgia and myalgias, as well as a non-purulent conjunctivitis. An important differentiator regarding the zika virus, is that it also appears to be highly neurotropic. Zika fever was believed to have been introduced into Latin America in 2014 (Haug, Kieny and Murgue, 2016). The biggest concern about zika virus infection stems from the 2015 alerts issued by the Pan American Health Organization (PAHO) of the WHO, specifically regarding a large number of cases of congenital birth defects, particularly microcephaly. It therefore appears that zika will join a growing list of NTD that disproportionally affect female reproductive health, such as Chagas disease, schistosomiasis and hookworm infection (Hotez and Askoy, 2016).

The Figure 3 shows the countries in which the NTDs occurs; the extensive geographic overlap of these conditions means that many of the NTDs are co-endemic and that it is common for poor people to be simultaneously infected with multiple NTDs. Among 56 nations with five or more endemic NTDs, 40 are found in Africa, 9 in Asia, 5 in the Americas and 2 in the Middle East. Today, Africa accounts for 100% of all of the world's few remaining cases of

dracunculiasis, 99% of the cases of onchocerciasis, more than 90% of the world's case of schistosomiasis, approximately 40% of the cases of lymphatic filariasis and trachoma, and one-third of the world's hookworm infections (Hotez, 2013).

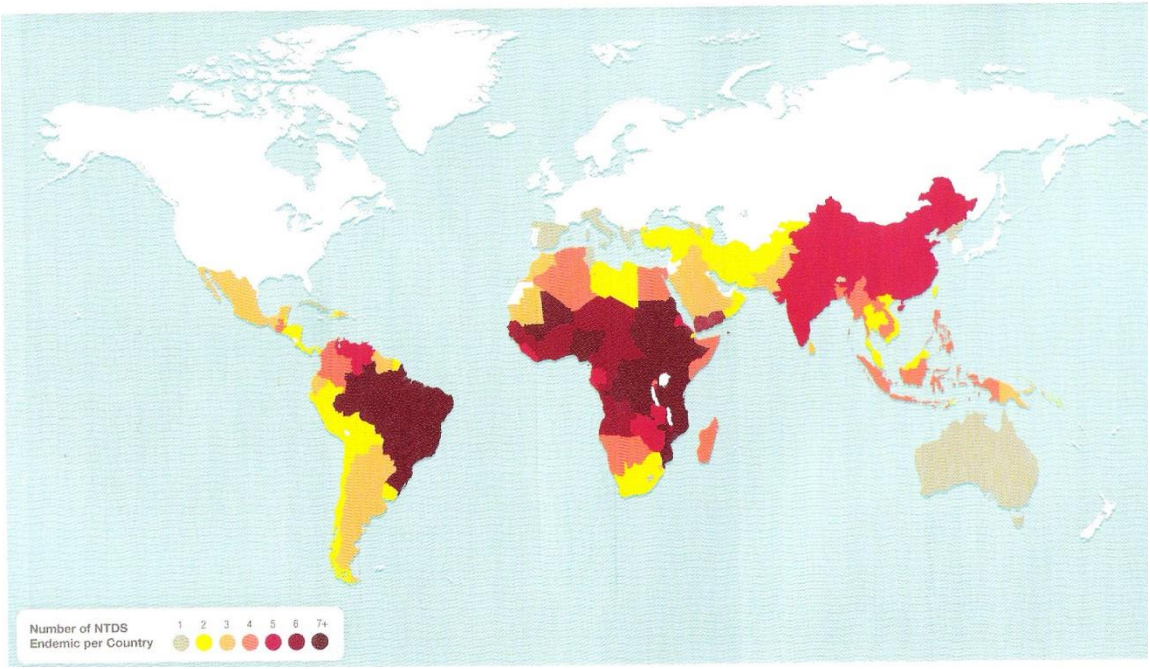


Figure 3 - Burden of NTDs (blinding trachoma, river blindness, Chagas disease, soil-transmitted helminth infections, guinea worm infection, schistosomiasis, sleeping sickness, visceral leishmaniosis, and lymphatic filariasis). This map displays countries where one or more of these diseases are endemic, based on 2009-2010 data (Hotez, 2013).

The major NTDs exhibit a remarkable set of features, all of which adversely affect the health and socioeconomic status of the world's poorest people (Hotez, 2013). These common features are presented and discussed below:

- The NTDs have **high prevalence** – as we have seen in Figure 3 the NTDs are among the most common infection of the poorest people in developing countries;
- The NTDs are linked to **rural poverty** – the NTDs are primarily found in poor rural and agricultural areas, particularly in regions where subsistence farming is practiced. Unlike HIV/SIDA or other better-known infections, the NTDs are often both out of sight and out of mind. They truly are forgotten diseases afflicting forgotten people;
- The NTDs are **ancient conditions** – NTDs are just the opposite of better-known emerging infections, such as avian influenza, SARS, Ebola, Lyme disease, and HIV/SIDA, which have either newly appeared in the population or have rapidly increased in incidence or geographic range;

- The NTDs are **chronic conditions** – Unlike many infectious diseases with which we are familiar, they are mostly chronic infections lasting years and sometimes even decades. In some cases, poor people can suffer from NTDs for their entire lives;
- The NTDs cause **disability and disfigurement** – NTDs frequently do not exhibit the classic features of most infections. They do not typically cause acute febrile illness which either resolve or kill. The NTDs mostly cause chronic conditions that lead to long-term disabilities and, in some cases, disfigurement;
- The NTDs are **stigmatizing** – the blinding and disfiguring features of NTDs are stigmatizing and cause individuals to be ostracized by their families, their communities, and sometimes even health care professionals. In some societies, NTDs are considered a sign of a curse or an "evil eye";
- The NTDs have high **disease burden but low mortality** – an estimated 530 000 people die annually from NTDs. These numbers pale in comparison to the number of annual deaths from HIV/AIDS which is 1-2 million deaths annually. Using the disability-adjusted life years (DALYs) which consider the number of healthy life years lost from either premature death or disability. Because of the chronic, disabling and disfiguring components of the NTDs, the DALYs ascribed to them are substantial (about 56.6 million DALYs annually);
- The NTDs have **poverty-promoting features** and other **socioeconomic consequences** – According Hotez the health impact of the NTDs may also represent only the tip of the iceberg in terms of their adverse effects on international development. The NTDs also produce important and serious socioeconomic consequences that keep affected populations mired in poverty. The NTDs not only occur in the setting of poverty; they also actually promote poverty. Reduced school attendance leads to reduce future wage-earning capacity, while chronic hookworm infection among agricultural workers has been shown to reduce worker productivity in Africa, Asia and the Americas (Hotez *et al.*, 2007).

Issues related to challenges, progress and opportunities concern with orphan medicines for patients who suffer of neglected tropical diseases will be discussed at chapter 7.

Chapter 2: Legal Background of Orphan Medicines

2.1 The History of Drug Legislation

Before orphan drug legislation was introduced, rare diseases were not a priority for the pharmaceutical and biotech industry, as it was not considered profitable to develop drugs for small patient cohorts. To bring a new pharmaceutical drug to the market is both time-consuming and very costly. The development of a new drug often includes several years of basic research to find a substance as a promising drug candidate. This is followed by studies on animals and clinical trials to provide data that must be reviewed and assessed before a drug is approved. To make a complicated procedure more complicated, often there are not *in vivo* animal models (Wizemann, Robinson and Giffin, 2009; Field and Boat, 2010; Hernberg-Sthal and Reljanovic, 2013).

It is interesting to note that the driving force behind the implementation of the orphan drug legislation, both in the USA and later on in Europe, was not the pharmaceutical industry, but rather patient organizations (Hernberg-Sthal and Reljanovic, 2013).

Thus, the creation of the interagency in USA, in 1978, came after hearings on the recommendations of a congressionally created (1977), Commission for the Control of Huntington's Disease and Its Consequences, calls for action from the Neurologic Drugs Advisory Committee of FDA, and pressure from other individuals and groups that were highlighting the barriers to the development of therapies for rare conditions and proposing government action to overcome these barriers (Field and Boat, 2010).

The pharmaceutical industry reportedly declined to participate in the Task Force on Drugs of Limited Commercial Value, but the Pharmaceutical Manufacturers Association (now the Pharmaceutical Research and Manufacturers of America) surveyed its member firms in 1978 and developed an inventory of company activities related to drugs for rare conditions (Field and Boat, 2010).

The 1979 interagency task force report proposed a voluntary program to encourage drug development by pharmaceutical companies, nonprofit organizations, or consortia. The federal government would act as a catalyst by providing some form of financial subsidy and by offering priority in the review of new drug approval applications. The report also mentioned the possibility of legislation creating tax and patent incentives (Field and Boat, 2010).

In the early 1980s several rare disease patient organizations in the USA worked diligently to highlight the lack of focus from industry in developing treatments for rare diseases. By utilizing different public relation approaches and working closely with reporters, attention in the USA was finally brought to bear on this disease area. The US congress and senate realized the huge unmet medical need for patients with rare disease and the orphan drug legislation was born (Hernberg-Sthal and Reljanovic, 2013).

The Orphan Drug Act (ODA) was signed into law by President Ronald Reagan in 1983 (Field and Boat, 2010; FDA, 2013; Hernberg-Sthal and Reljanovic, 2013). The objective of the ODA was to encourage the pharmaceutical industry and to stimulate it to overcome the various hurdles in developing orphan drugs, which is discussed in more detail below. Also in 1983, several individuals formed the National Organization for Rare Diseases (NORD) (Field and Boat, 2010; Hernberg-Sthal and Reljanovic, 2013), whose role will discussed in 3rd chapter.

Once the ODA had become law in the USA, other countries followed its example: legislation was introduced in Singapore in the 1991 "Medicine (Orphan Drug) Exemption order", in Japan in 1993 with a revision of the Pharmaceutical Affairs Law, in Australia at 1997 (establishing their orphan drugs policy), in 1998 in Korea (which established the Korean Orphan Drug Centre) and Taiwan in 2000 with the Rare Diseases and Orphan Drug Act (Hernberg-Sthal and Reljanovic, 2013).

At the pan-European level, one of the first steps in addressing the question of orphan drugs was issued in the European Council Resolution of 20 December 1995 (95/C 350/03), which considered the following aspects (Hernberg-Sthal and Reljanovic, 2013):

- Definition of "orphan" drug;
- Definition of "rare" disease;
- Criteria for obtaining "orphan" drug status;
- Regulatory provisions and financial incentives to promote research, development and marketing authorization of orphan drugs;
- Examination of health impact of a European policy on orphan drugs in the Member States.

The European Parliament and Council adopted the regulation on Orphan Medicinal Products in December 1999, and in April 2000 the regulation was adopted by the European Commission (European Commission, 2000).

2.2 Food and Drug Administration

Food and Drug Administration (FDA) is responsible for protecting the public health, in United States of America, by assuring safety, efficacy and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer and more affordable (FDA, 2014).

2.2.1 United States of America Definition

According the US Food and Drug Administration, an orphan drug is (FDA, 2016):

- Intended to treat a disease or condition which affecting fewer than 200,000 persons in US or
- Intended to treat a disease or condition which affecting more than 200,000 persons in US, but for which there is no reasonable expectation that the sales of the drug treatment will recover the costs.

2.2.2 Orphan Drug Act

The original purpose of the 1983 Orphan Drug Act was to provide incentives in the development of drugs for the treatment of rare diseases that would normally be unprofitable or not patentable. The ODA charged the FDA with the role of reviewing and approving request for orphan product designation, overseeing the seven years exclusive marketing for orphan products, coordinating research study design assistance for sponsors of orphan drugs, encouraging sponsors to conduct open protocols, and awarding grants for development of orphan drugs. The functions are performed by the FDA Office of Orphan Products Development (OOPD). An amendment to the Act in 1984 established a numeric prevalence threshold to the definition of a rare disease or condition. To qualify for orphan drug status, a rare disease or condition was defined as any disease or condition (1) affecting less than 200,000 persons in US or (2) affecting more than 200,000 persons in US, but for which there is no reasonable expectation that the sales of the drug treatment will recover the costs. In 1985, the Act was amended again, this time to extend marketing exclusivity for both patentable and

not patentable products. In 1988, an amendment to the Act changed the requirement for submitting applications for orphan drug status. Under the revised Act, the application for Orphan Drug Designation now has to be made prior to the submission of an application for marketing approval, New Drug Application (NDA) or Product License Application (PLA) (Gottlober, 2001; Villarreal, 2001; Seoane-Vazquez *et al.*, 2008; Wilding *et al.*, 2013).

2.2.3 How to Apply for Orphan Designation

A sponsor may request orphan-drug designation of a previously unapproved drug or of a new use for an already marketed drug (FDA, 2015).

The sponsor that submits a request for orphan drug designation of a specific rare disease shall submit each request in the form and two copies of a completed, dated, and signed request for a designation that contains (FDA, 2015):

- A statement that the sponsor requests orphan-drug designation for a rare disease, which shall be identified with specificity;
- The name and address, telephone number, and email address; 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;
- 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;
- 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 condition, including *in vitro* and *in vivo* studies and clinical experience with the drug in the rare disease;
- If the same drug is already approved, an explanation of why the purposed variation may be clinically superior to the first drug;
- If a sponsor request orphan-drug designation for a drug intended for only a subset of persons with a particular disease that affects 200,000 or more people, a demonstration

that, due to one or more properties of the drug, the remaining persons with such disease would not be appropriate candidates for use of the drug;

- A summary of the regulatory status and marketing history of the drug in US and in foreign countries (marketing application status, 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);
- Documentation, with appended authoritative references, to demonstrate that:
    i. The disease for which the drug is intended affects fewer than 200,000 people in US or if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the US are fewer than 200,000 per year.
    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 US, 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 US.

Although the Office's policy is that it will try to respond within **60 days** of receiving an application for orphan designation, the process may take longer if the office needs more information from the sponsor. After receiving the orphan designation and conducting more research, a sponsor may seek marketing approval if the drug proves safe and effective in clinical trials. The office plays no formal role in the decision to approve a drug; CDER and CBER have this responsibility (FDA, 2010, 2013).

2.2.4 Economic Assistance and Incentives for Drug Development

Congress passed the Orphan Drug Act of 1983 to stimulate the development of drugs for rare diseases. Prior to passage of this historic legislation, private industry had little incentive to invest money in the development of treatments for small patient populations, because the drugs were expected to be unprofitable. The law provides following **incentives** (Gottlober, 2001):

- 7-year market exclusivity to sponsors of approved orphan products;
- A tax credit of 50 percent of the cost of conducting human clinical trials;

- Federal research grants for clinical testing of new therapies to treat and/or diagnose rare diseases;
- Fast-track development and approval;
- Waived drug application fees.

The program has successfully enabled the development and marketing close of 500 drugs and biologic products for rare diseases from 1983 to 2015. In contrast, fewer than 10 such products supported by industry came to market between 1973 and 1983 (FDA, 2015).

During the first 25-years history of OOPD, the program has been successful, granting more than 1,850 orphan drug designations, 326 of which have received full FDA marketing approval between 1983 and 2008 (Wizemann, Robinson and Giffin, 2009).

Figure 4 and Figure 5 show, respectively, the number of orphan drug designation requests and the number of approved orphan products, between 1983 and 2014, in US.

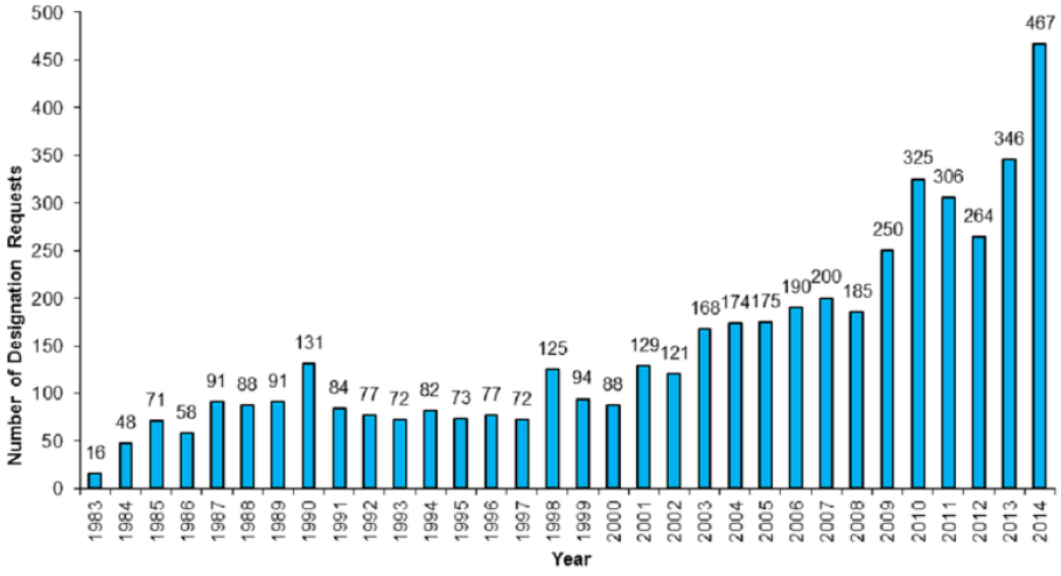


Figure 4 - Number of Orphan Drug Designation Requests by year in US. Adapted from (Public Citizen, 2015)**.**

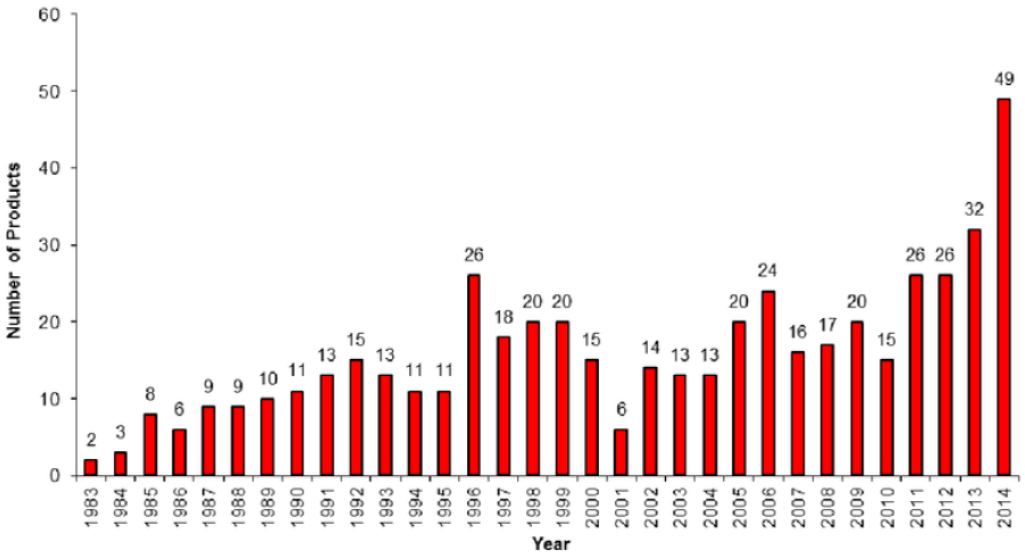


Figure 5 - Number of Approved Orphan Products by year in US. Adapted from (Public Citizen, 2015)**.**

The OOPD administers two extramural grant programs: the **Orphan Products Grants Program** provides funding for clinical research that tests the safety and efficacy of drugs, biologics, medical devices and medical foods in rare diseases or conditions; the **Paediatric Device Consortia (PDC) Grant Program** provides funding to develop non-profit consortia to facilitate pediatric medical device development (FDA, 2016)**.**

2.2.5 Rare Pediatric Disease Priority Review Vouchers

Rare Pediatric Disease Priority Review Voucher (PRV) was created in 2012 under FDA Safety and Innovations Act (FDASIA) to encourage development of drugs or biologics for prevention and treatment of rare pediatric diseases. Such drug/biologic may not contain any active ingredient previously approved in any drug or biologic application (FDA, 2014).

The FDASIA added Section 529 to the Federal Food, Drug, and Cosmetic Act. Pursuant to that provision, FDA will award priority review vouchers to sponsors of rare pediatric disease product applications that meet certain criteria. Section 529 provides an additional incentive for rare pediatric diseases, which may be used alone or in combination with other incentive programs: orphan drug designation, under Orphan Drug Act, and programs that encourage or require the study of drugs used in pediatric population, under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) (FDA, 2014).

If a sponsor receives approval of a rare pediatric disease product application for a rare pediatric disease, the sponsor is eligible to receive a PRV which can be redeemed, or transferred to another sponsor, to obtain priority review of another application that would otherwise be ineligible for priority review (FDA, 2014).

A rare pediatric disease is defined at a section 529(a)(3) as a disease that:

- "Primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents," which FDA interprets as meaning that greater than 50% of the affected population in the U.S. is aged 0 through 18 years **and**
- Is "rare disease or condition" as defined in section 526 of the Federal Food, Drug and Cosmetic Act.

2.3 European Medicines Agency

The European Medicines Agency (EMA) is a decentralized body of the European Union (EU), located in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The Agency is responsible for the scientific evaluation of applications for European Union marketing authorizations for human and veterinary medicines in a centralized procedure. Under this procedure, companies submit a single marketing-authorization application to the Agency. Once granted by the European Commission, a centralized marketing authorization is valid in all European Union and EEA-EFTA States (Iceland, Liechtenstein and Norway) (EMA, 2016). The centralized procedure is compulsory for (EMA, 2016):

- human medicines for treatment of human immunodeficiency virus (HIV) or acquired deficiency syndrome (AIDS),
- cancer,
- diabetes,
- neurodegenerative diseases,
- auto-immune and other immune dysfunctions, and
- viral diseases;
- veterinary medicines for use as growth or yield enhancers;

- medicines derived from biotechnology processes; advanced-therapy medicines, such as gene-therapy, somatic cell-therapy; and
- officially designated '**orphan medicines'.**

Legislation on orphan medicinal products, in Europe, entered into force in January 2000 with **Regulation (EC) No 141/2000** of the European Parliament and of the Council (European Commission, 2000) and **Commission Regulation (EC) No 847/2000** in April 2000 (European Commission, 2000). This introduced a procedure for the designation of medicines as orphan medicinal products and incentives for their development and placement on the market.

Since 2000, there is a Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency. The COMP is comprised of health professionals representing each of the Member States (ate the moment, there are 28), three patient representatives, and another three representatives nominated by the EC. The Committee meets once a month and it's responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of orphan diseases. The Commission adopts decisions on designation based on an opinion from the COMP. Since its implementation and till 2014, the Orphan Regulation has yield more than 1230 positive opinions for orphan product designation, adopted from more than 1789 applications reviewed (Rodwell and Aymé, 2014).

2.3.1 European Definition

According to the EMA, a medicinal product is designated as an orphan medicinal product if (EMA, 2007):

- it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 persons in the European Union at the time of submission of the designation application (prevalence criterion), or;
- it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and that without incentives is unlikely that expected sales of the medicinal product would cover the investment in its development (seriousness criterion), and;

- no satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorized, or, if such method exists, the medicinal product will be of significant benefit to those affected by the condition.

2.3.2 Orphan Incentives

In the European Union, the legislation provides incentives for pharmaceutical industry to develop orphan medicinal products (EMA, 2013). To be eligible for incentives, products should be designated through the procedure for orphan designation:

- **Market exclusivity**

For 10 years (+2 if pediatric) after the granting of a marketing authorization (MA), approval for sale, orphan medicinal products benefit from market exclusivity in the EU. During that period, directly competitive similar products cannot normally be placed on the market (EMA, 2013).

- **Protocol assistance**

The European Medicines Agency can provide scientific advice (SA) and protocol assistance (PA) to optimize development and guidance on preparing a dossier that will meet European regulatory requirements. This helps applicants to maximize the chances of their marketing authorization application being successful (European Commission, 2006).

Protocol assistance requests should contain prospective questions concerning quality (chemical, pharmaceutical and biological testing), preclinical (toxicological and pharmacological tests), and clinical aspects (studies in human subjects in either patients or healthy volunteers, including clinical pharmacological trials designed to determine the efficacy and safety of the product for pre or post–Authorization activities) relating to the proposed future development of the medicinal product (European Commission, 2006).

Protocol assistance requests are validated by a scientific administrator appointed by the EMA. Once validated, the request will be forwarded to Scientific Advice Working Party (SAWP) members and an invoice of the fee to be paid will be sent to the billing address indicated by the applicant. The scientific advice or protocol assistance provided to companies is the result of a collegial work from the Co-ordinators, the SAWP, the experts, the various Working

Parties and Scientific Advisory Groups, the CHMP and the COMP (for questions related to demonstration of significant benefit within the scope of protocol assistance). The answer is prepared by the Co-ordinators and then submitted to the relevant Working Parties for comments and to the SAWP for discussion and adoption of a common position before being forwarded to the CHMP and/or the COMP for formal adoption. The type of procedures (simplified or standard) will be determined on a case-by-case basis (European Commission, 2006). The Figure 6 shows a diagram with an overview of the Protocol Assistance procedures.

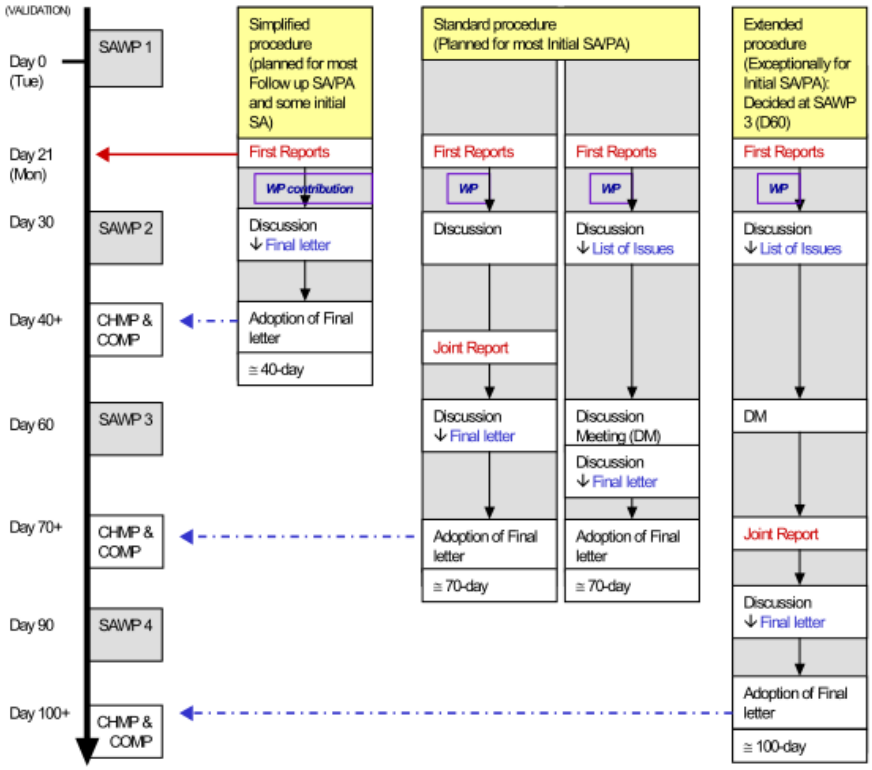


Figure 6 - Overview over the Scientific Advice/Protocol Assistance Procedures (European Commission, 2006).

- **Fee reductions**

A special fund from the European Commission, agreed annually by the European Parliament, is used by the Agency to Grant fee reductions. Reduction of fees will be considered for various centralized activities, including applications for marketing authorization, inspections and protocol assistance. Additional fee reductions apply for small and medium-sized enterprises (SMEs) (EMA, 2013):

- 75% fee reduction (100% for SMEs) on Protocol Assistance, initial and follow-up requests, 100% for paediatric-related assistance;
- 10% fee reduction (100% for SMEs) on Marketing Authorization Application;
- 100% fee reduction for Inspections;
- 100% fee reduction for SMEs on Post authorization application and annual fee, in the first year from granting of a marketing authorization

- **EU-funded research**

Sponsors developing orphan medicinal products may be eligible for grants from EU and Member State programs and initiatives supporting research and development, including the Commission's framework program (EMA, 2013).

2.3.3 How to Apply for Orphan Designation

A sponsor may apply for designation of a medicinal product as an orphan medicinal product for an already approved medicinal product provided the orphan designation concerns an unapproved therapeutic indication.

First, sponsors should notify the EMA of their intention to submit an application, at least two months prior to the planned submission date. This notification should be include (European Commission, 2014):

- The name of the active substance;
- The proposed orphan indication;
- The name and address of the sponsor;
- The planned submission date for the designation application and the proposed date for a pre-submission meeting (if required);
- The unique product identifier (UPI number).

EMA encourages sponsors to request a pre-submission meeting prior to filling application. These meetings can take place via teleconference. Where possible, sponsors should request a pre-submission meeting ate least two months prior to filling. Pre-submission meetings for orphan designation are free of charge and experience has shown that they have a positive impact on the success rate of the applications (European Commission, 2014).

Then, sponsors should submit the application to EMA, via Eudralink. The complete application should include (European Commission, 2014):

- Cover letter;
- EMA application form;
- Scientific sections A-E of the application;
- Proof of establishment of the sponsor in the EU;
- Letter of authorization from the sponsor for the company acting on their behalf, if applicable;
- Translations of the name of the product and the proposed indication into the official languages of the EU (also Icelandic and Norwegian);
- Bibliography.

The EMA secretariat will complete the validation of the application. The sponsor will receive a validation issues letter and will be asked to respond within a 3-month time limit. Once validation process is successfully completed, a timetable to start the procedure for the evaluation will be forwarded to the sponsor for information (European Commission, 2014).

During the evaluation phase the EMA coordinator will work very closely with the COMP coordinator and appointed experts. They will prepare a summary report on the application which includes data reported in the sponsor's application, a critical review and a conclusion. The summary report will be circulated to the COMP members for comments. Following the COMP's first discussion the sponsor may be invited to address the list of questions at next meeting (European Commission, 2014).

Before day 90, the COMP adopts its opinion (in English). The information on the adopted COMP opinions is published on the EMA website. The sponsor is requested to confirm in writing (via e-mail) the receipt of the COMP opinion. The decision will be adopted by the Commission within 30 days from reception of the COMP opinion. The designated medicinal product shall be entered in the Community Register of Orphan Medicinal Products (European Commission, 2014).

The following scheme shows the orphan designation procedure (Figure 7).

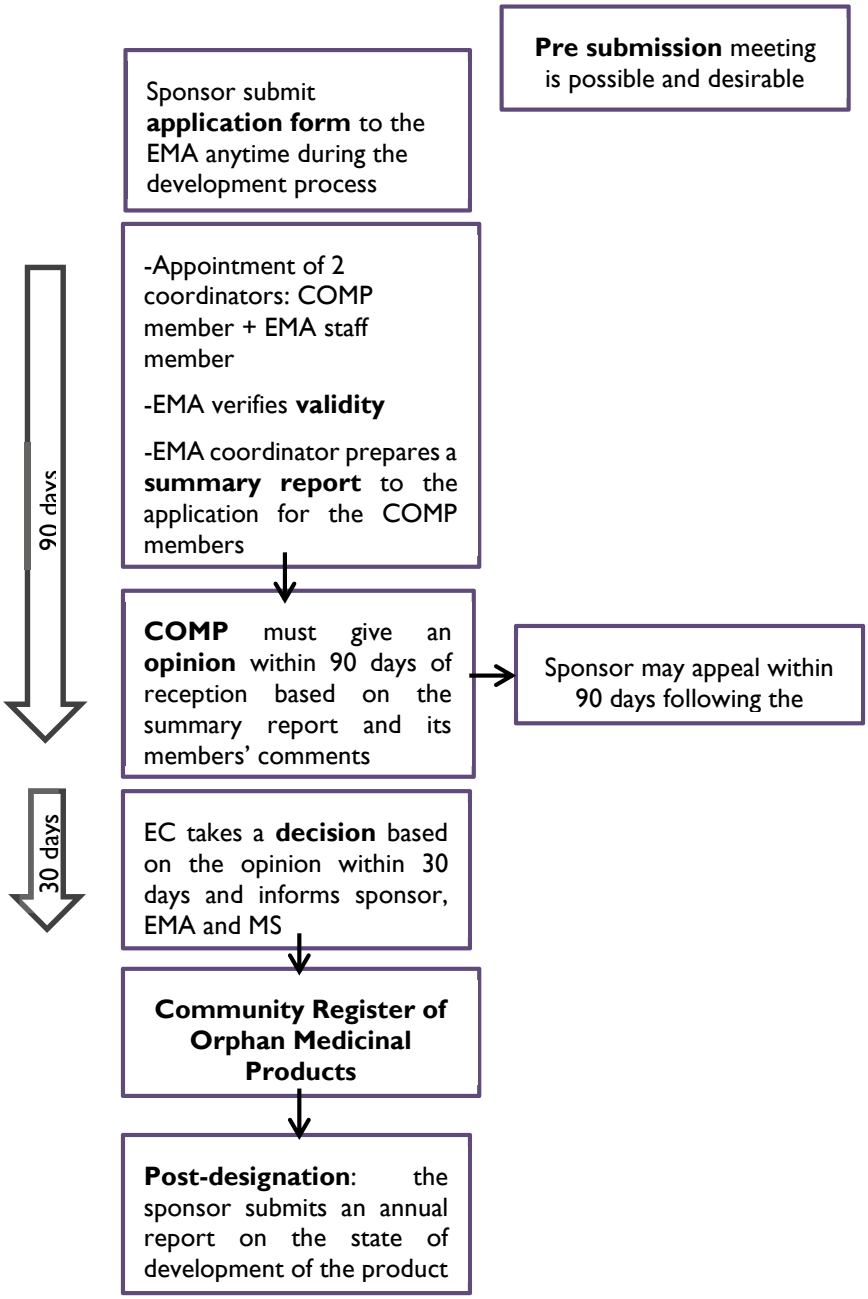


Figure 7 - Orphan Designation Procedure. Adapted from (Federaal Kenniscentrum voor de Gezondheidszorg, 2009)**.**

2.3.4 Removal of Orphan Designation

According with Article 5(12) of the Orphan Regulation, "a designated orphan medicinal product shall be removed at the request of the sponsor, if it is established before the MA is granted that the criteria for designation are no longer met or at the end of the period of market exclusivity".

To request removal, the sponsor should (European Commission, 2000):

- Prepare a letter requesting removal of the orphan designation, signed by a person having the legal mandate to request a removal;
- Send a PDF version of the letter to the European Commission.

The removal of an orphan designation from the Community register is irreversible (European Commission, 2000).

After removal of an orphan designation, the Agency will update its published information to reflect the fact that the orphan designation has been removed from the Community register at the request of the sponsor (European Commission, 2000).

The responsibility for assessing the criteria for orphan designation rests solely with the COMP, which is responsible for giving a scientific opinion on the initial designation (European Commission, 2000). Thus, if the Commission decides, following the opinion of the COMP, that the criteria in which the original decision was based are no longer met, the drug will be removed from the Community register.

2.3.5 Market Authorization and Market Exclusivity

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 lays down a centralized community procedure for the authorization of medicinal products, for which there is a single application, a single evaluation and a single authorization allowing direct access to the single market of the Community.

For medicines (orphan and non-orphan) to be approved at the EU Community level a dossier must be submitted to the Committee for Medicinal Products for Human Use (CHMP). This committee is responsible for evaluating the data presented to determine whether they are sufficient to permit market authorization (see Figure 8) (European Commission, 2006).

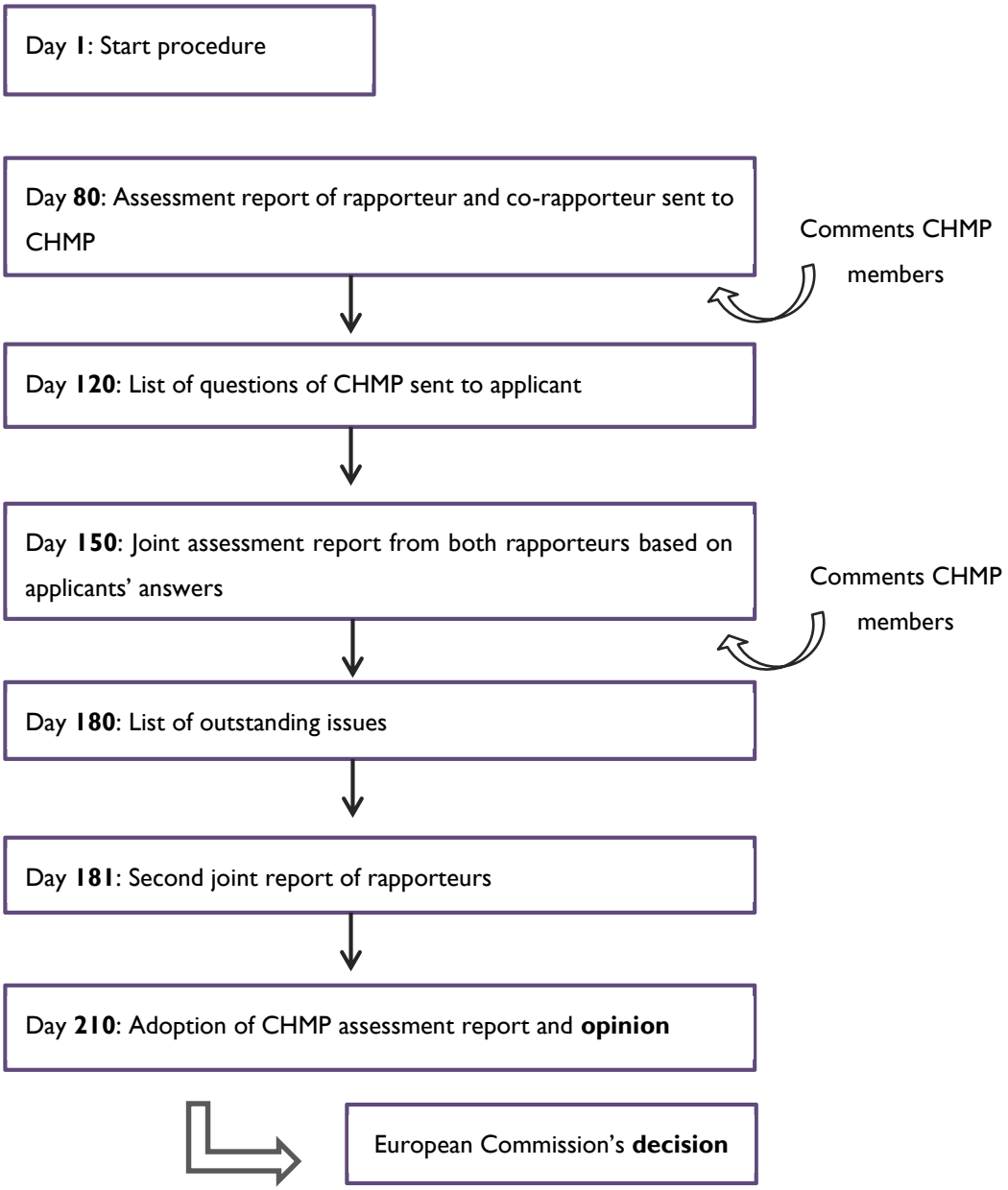


Figure 8 - Centralized Procedure for Marketing Authorization. Adapted from (Federaal Kenniscentrum voor de Gezondheidszorg, 2009).

2.3.6 Orphan Medicines in Pediatric Population in EU

It is known that the use of unlicensed and off-label medicines, widespread among children affected by rare diseases resulted in inefficacy and serious side effects due to incorrect dosage (Dunne, 2007). To counteract this, the EU Regulation on Pediatric Drugs was adopted by the European and the Council of Ministers in 2006 (*Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006*) after many years of advocacy work by stakeholders with EURORDIS at the forefront.

In fact, according Diseases and Countries in Europe, many medicines (50 to 90%) administered to children have not been developed for them and are administered to children by decreasing quantities based on weight, which is extremely hazardous (EURORDIS, 2012).

Based on that, the EU regulation established (The European Parliament and The Council of the European Union, 2006):

- an obligation of paediatric research (Paediatric Investigation Plan – PIP) for every new drug developed for adults and having a potential use for children;
- creation of an inventory of specific needs for paediatric medicinal products;
- creation of a paediatric committee including patient representatives at the EMA;
- six months extension of the patent for the paediatric formula of existing 'still under-protection' adult medicine;
- two years extension of market exclusivity for orphan drugs for children (12 years in total);
- financial support via the EU research Framework Program for Research on old (off-patent) drugs to study and develop paediatric use;
- implementation of a process to avoid unnecessary clinical studies on children;
- specific label products studied in children and authorized: the Paediatric Use Marketing Authorization (PUMA)

2.3.7 List of orphan medicinal products in Europe with European orphan designation and European marketing authorization:

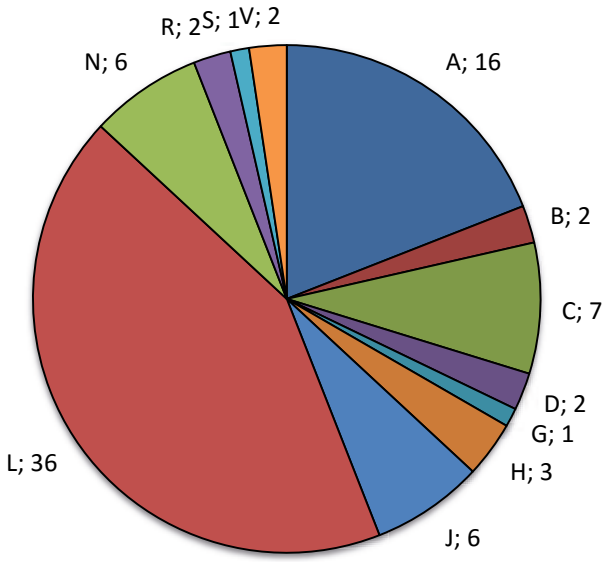
Classification by ATC category

Table 5 - Orphan medicines with European marketing authorization(Orphanet, 2015).

A. Alimentary tract and Metabolism	**D. Dermatologicals**	Dacogen®	Vidaza®
Carbaglu®	Nexobrid®	Esbriet®	Votubia®
Cerdelga®	Scenesse®	Evoltra®	Xagrid®
Cystadine®	**G. Genito Urinary System and Sex hormones**	Gazyvaro®	Xaluprine®
Elaprase®	Revatio®	Gliolan®	Yondelis®
Kolbam®	**H. Systemic hormonal preparations***	Iclusig®	**N. Nervous system**
Kuvan®	Increlex®	Imbruvica®	Diacomit®
Myozyme®	Plenadren®	Imnovid®	Firdapse®
Naglazyme®	Signifor®	Jakavi®	Inovelon®
Orfadin®	**J. General antiinfectives for systemic use**	Litak®	Peyona®
Orphacol®	Cayston®	Lynparza®	Inovelon®
Procysbi®	Deltyba®	Lysodren®	Peyona®
Revestive®	Ketoconazole®	Mepact®	Prialt®
Vimizim®	Para aminoacid lucane®	Mozobil®	
Vpriv®	Sirturo®	Nexavar®	Vyndaqel®
Wilzin®	Tobi Podhaler®	Ofev®	**R. Respiratory system**
Zavesca®	**L. Antineoplastic and immunomodulating agents**	Revlimid®	Bronchitol®
B. Blood and Forming Organs	Adcetris®	Siklos®	Kalydeco®
Defitelio®	Arzerra®	Soliris®	**S. Sensory Organs**
Nplate®	Atriance®	Sprycel®	Holoclar®
C. Cardiovascular System	Bosulif®	Tasigna®	**V. Various**
Adempas®	Ceplene®	Tepadina®	Exjade®
Firazyr®	Cometriq®	Thalidomide Celgene®	**ATC code not yet assigned**
Glybera®	Cyramza®	Torisel®	Sylvant®;Translarna®

*excluding sex hormones and insulins

As the Graphic 1 shows, most drugs with orphan drug designation belongs to a class L – Antineoplastic and immunomodulating agents (Orphanet, 2015).



Graphic 1 - Number of orphan medicinal products in Europe with European orphan designation and European Marketing Authorization (Orphanet, 2015).

2.4 Legislation and the Definition of Orphan Diseases in Different Countries

Despite the fact that this dissertation focus particularly on the American and European legislation, it is interesting to compare some regulatory aspects between USA, European Union and other countries in the world (Table 6).

Table 6 - Features of orphan drugs incentives systems in USA, EU, Japan and Australia (European Commission, 2000; Seoane-Vazquez *et al.*, 2008; Jambhekar, 2011).

Parameters	USA	EU	Japan	Australia
Legal Framework	Orphan Drug Act (1983)	Regulation (CE) N°141/2000	Orphan Drug Regulation (1993)	Orphan Drug Policy (1998)
Administrative Authorities	FDA/OOPD	EMA/COMP	Ministry of Labor and Welfare (MHLW) Orphan Drug Division	TGA

Parameters	USA	EU	Japan	Australia
Prevalence criteria (per 10,000)	7.5	5	4	1.1
Prevalence rate	20 millions	25-30 millions	No information	No information
Market Exclusivity	7 years	10 years	10 years	5 years
Tax Credit	50% for clinical studies	Managed by the member states	6% for any type of study + limited to 10% of the company's corporation tax	No
Grants for research	NIH Programs and others	Horizon 2020	Governmental funds	No
Technical Assistance	Yes FDA meetings	Yes Protocol Assistance	Upon request	Upon request
Accelerated Marketing procedure	Yes	Yes	Yes	Yes

Chapter 3: Patient Network and Advocacy Groups

Patient organizations have many important roles in the field of rare diseases: they increase public awareness, collect information about rare diseases, provide support and information to affected families, encourage basic research and grant funds, maintain patient registries and collections of specimens in biobanks, and network with universities, industry and health authorities (Hernberg-Sthal and Reljanovic, 2013).

The biggest umbrella patient organizations are EURORDIS in Europe and NORD in the USA. Recently, these two groups have signed a strategic partnership agreement to align their activities more effectively (Hernberg-Sthal and Reljanovic, 2013).

3.1 Umbrella Organizations: EURORDIS and NORD

3.1.1 European Rare Diseases Organization (EURORDIS)

According to their website EURORDIS is "a non-governmental patient-driven alliance of patient organizations and individuals active in the field of rare diseases, dedicated to improving the quality of life of all people living with rare diseases in Europe" (EURORDIS, 2016).

The mission is to build a strong pan-European community of patient organizations and of the people living with rare diseases, to be their voice at the European level and to fight against the impact of rare diseases on affected patients' lives (Hernberg-Sthal and Reljanovic, 2013; EURORDIS, 2016). EURORDIS seeks to improve the quality of life of people living with rare diseases in Europe through advocacy at the European level, support for research and medicines development, facilitating networking amongst patient groups, raising awareness, and many other actions designed to reduce the impact of rare diseases on the lives of patients and family (EURORDIS, 2016).

The following table shows the activities performed by EURORDIS (Table 7).

Table 7 - Six major areas of activity of EURORDIS and some examples.

Role	Examples of Activities
Advocating for Patients: EURORDIS represents 30 million patients affected by over 5000 distinct rare (EURORDIS, 2014).	• Promotion of National Plans and Strategies on Rare; Diseases in all 28 EU Member States and other European countries; • Organization of the **European Conferences on Rare Diseases (ECRD);** • Organization of the International Rare Disease Day
Health Policy and Health Services: Active role in the processes to develop and implement national and European-level policies that bring real solutions to people living with rare diseases (EURORDIS, 2014).	• EURORDIS has representatives at the EUCERD and is a partner of the European Union Committee of Experts on Rare Diseases (EUCERD) Joint Action; • Through the EUCERD Joint Action and its EUROPLAN Work Package, EURORDIS facilitates the organization of the EUROPLAN National Conferences.
Medicines and Therapies: Member of relevant scientific committees, namely COMP (EURORDIS, 2014).	• Involvement in EU policies; • Reviews all public summaries of **COMP** opinion documents on applications for orphan drugs; • Involved in several initiatives to improve access to rare disease medicines across Europe: **Clinical Added Value of Orphan Medicinal Products (CAVOMP)** and **Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA).**
Research Policy and Actions: Promotes rare disease research and has developed distinct position papers that delineate the expectations of the rare disease community (EURORDIS, 2014).	• Actively involved in the **International Rare Diseases Research Consortium (IRDiRC)** Executive Committee, Scientific Committees and Working Groups. Provides inputs and support to its IRDiRC representatives, contributing to policy documents; • One of 27 full partners in **RD-Connect** EURORDIS is one of 11 partners in the **EPIRARE** project
Patient Empowerment and Training: EURORDIS' training programs and resources are designed to strengthen the capacity of rare disease patients' representatives (EURORDIS, 2014).	• Annual EURORDIS Summer School to empower people living with rare disease and online learning courses about clinical trials (methodology, ethics and statistics); • EURORDIS is a partner in the **European Patients'Academy on Therapeutic Innovation (EUPATI)** – an Innovative Medicines Initiative (IMI) and European Federation of Pharmaceutical Industries and Associations (EFPIA).

Role	Examples of Activities
Information and Networking: EURORDIS has 695 member organizations in 63 countries, representing altogether more than 4000 different diseases. (EURORDIS, 2014).	• EURORDIS call for a **European Year for Rare Diseases (2019)**

EURORDIS collaborates with NORD and other patient organizations such as Canadian Organization for Rare Disorders (CORD), at the international level (Hernberg-Sthal and Reljanovic, 2013).

3.1.2 National Organization for Rare Disorders (NORD)

NORD is the US federation of voluntary health organizations helping people with rare diseases. As mentioned in 2.1, NORD was established in 1983 by patients who worked together to get the Orphan Drug Act passed (Field and Boat, 2010; Hernberg-Sthal and Reljanovic, 2013).

According to their website, NORD is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services (NORD, 2015).

NORD, along with its more than 230 patient organization members is dedicated to helping the nearly 30 million Americans with rare diseases, and the organizations that serve them through programs of education, advocacy, research and patient services (Hernberg-Sthal and Reljanovic, 2013).

The ultimate goal of NORDS' activities is to improve the lives of individuals and families affected by rare diseases (NORD, 2015). There are 6 major areas of activities performed by NORD (NORD, 2015):

- **Patient Advocacy:**

  Since 1983, NORD has ensured that the rare disease perspective is at the table when important decisions are made. NORD's policy team works with policy makers on Capitol Hill, in White House, in government agencies, and at the local level to help inform policies that are reflective of the needs of rare disease patients.
- **Patient and Professional Education:**

  NORD provides information about rare diseases, patient organizations and other resources for patients and families.
- **Patient Assistance Program(PAP):**

  NORD pioneered Patient Assistance Programs in 1987 and we the leader in patient-focused PAPs today. NORD programs include free drug, co-pay and premium assistance, travel/loading assistance for clinical trials, and expanded or emergency access.
- **Mentorship for patient organizations:**

  Disease-specific patient organizations are crucial partners in NORD's mission to serve rare disease patients and their families. NORD provides capacity building and mentorship services to start-up and established organizations through one-on-one guidance, webinars, in-person meetings, and toolkits to help establish, strengthen and grow.
- **Research support:**

  Since 1989, NORD has administered a Research Program through which we provide grants that have resulted in numerous published advances and at least two FDA-approved therapies.
- **International Partnerships:**

  NORD has strategic partnership with international umbrella organization, such EURORDIS, has mentioned in 3.1.1.

3.2 European Organizations and Networks

3.2.1 Orphanet

Orphanet is the reference portal for information on rare diseases and orphan drugs, for all audiences. Orphanet's aim is to help improve the diagnosis, care and treatment of patients with rare diseases (Orphanet, 2015).

Orphanet offers a range of freely accessible services (Orphanet, 2015):

- An inventory and a classification of rare diseases, including prevalence and cross-referenced genetic information with Human Genome Organization Gene Nomenclature Committee (HGNC), GenAtlas and SwissProt;
- A RareDDB repository for rare disease or orphan disease, which provides detailed information for different types of rare diseases with their associated genes, single nucleotide polymorphisms (SNPs) along with functional annotations and drug's information; The RareDDB database was developed using information from various databases such Growth Hormone Receptor (GHR), Online Mendelian Inheritance in Man (OMIM), Resistance Database Initiative (RDI) and Short Genetic Variation (dbSNP) database (Badapanda, Gupta and Chikara, 2016);
- An encyclopedia of rare diseases;
- An inventory of orphan drugs at all stages of development from EMA's orphan drug designation to marketing authorization;
- A searchable directory of disease-related services (specialized medical facilities, diagnostic laboratories, research activities, clinical trials, patient registries, advocacy organizations);
- An assistance to diagnosis tool allowing users to search by signs and symptoms;
- Guidelines for emergency medical care and anesthesia;
- A fortnightly newsletter, OrphaNews, which gives an overview of scientific and political current affairs in field of rare diseases and orphan drugs;
- Orphanet Report Series (list of orphan drugs in Europe, Disease Registries in Europe, Prevalence Diseases).

The public database was initiated by National Institute of Health and Medical Research, France (INSERM) and is today maintained by a European consortium of 38 participating countries, coordinated by France and today is maintained by a European consortium of 38 participating countries, coordinated by France (Orphanet, 2015).

Orphanet is governed by various committees: the Steering Committee of representatives from the agencies and bodies that finance Orphanet, the Management Board made up of Orphanet country coordinators, and the International advisory Board consisting of approximately 100 international experts. National teams are responsible for the collection of information on

specialized clinics, medical laboratories, ongoing research and patient organizations in their country (Hernberg-Sthal and Reljanovic, 2013; Orphanet, 2015).

Orphanet provides the opportunity to patient groups to create their own web presentation. After registration in the database, patients may get in contact with organizations of other patients suffering from the same rare disease (Hernberg-Sthal and Reljanovic, 2013; Orphanet, 2015).

3.2.2 European Platform for Patient Organizations, Science and Industry (EPPOSI)

Founded in 1994, the European Platform for Patients' Organizations, Science and Industry (Epposi) is an independent, not-for-profit, partnership-based multi-stakeholder organization based in Brussels, Belgium. Epposi's mission is to provide a consensus-driven multi-stakeholder perspective from European patient organizations, science and industry to improve European public health outcomes (EPPOSI, 2015).

Through knowledge-exchange, dissemination of information and research, Epposi provides equally-weighted outcomes among all members. The outcomes are shared with a broader EU through events, meetings, and publications (EPPOSI, 2015).

Epposi is open to members from EU umbrella patient organizations, commercial enterprises and their related trade bodies, including research institutes, professional and business federations. Associate membership is also open to NGOs, active in healthcare foundations and international organizations, which want to support and benefit from Epposi ethos, and are also interested in representing a broad range of civil society needs (EPPOSI, 2015).

EURORDIS represents the patient with rare diseases within EPPOSI. A total of 18 large pharmaceutical and biotechnology companies and manufacturers of medical devices as well as five industrial associations are members of EPPOSI. Members of scientific organizations include the European Society of Human Genetics, the Amsterdam Lysosome Center, Cancer Research UK, the European Society for Clinical Investigations, the Union of European Medical Specialists, the Regulatory Affairs Professionals Society and others (Hernberg-Sthal and Reljanovic, 2013).

Currently, EPPOSI is focusing on four research areas through its Advanced Innovation Programs (AIP) (Hernberg-Sthal and Reljanovic, 2013):

- Chronic conditions management (AIP-CCM);
- Health technology assessment (AIP-HTA);
- **Rare diseases (AIP-RD)**

The key objective of AIP-RD is to build on EPPOSI's long-established work in the rare diseases arena to focus on specific areas where its multistakeholder perspective can complement the actions of existing and new partners in the field. Rare disease activities within EPPOSI are structures as the EPPOSI Rare Diseases Interest Group (RDIG). Its main mandate is to suggest project topics and to address rare disease issues in other programs. Current projects are to address the specificity of Rare Disease Challenges from a multistakeholder perspective on a minimum of two discrete rare disease policy projects such as the impact of ageing and neonatal screening (Hernberg-Sthal and Reljanovic, 2013).

3.2.3 Patients Network for Medical Research and Health - EGAN

According to their website The Patients Network for Medical Research and Health EGAN is an alliance of both National Genetic Alliances and European disease specific patient organizations with a special interest in genetics, genomics and biotechnology. Especially, but not only, genetic disorders are represented within EGAN (EGAN, 2015).

EGAN is working for a voice in research and health policy and seeks a world in which genetic and other serious diseases are understood, effectively treated, prevented and the people affected supported (EGAN, 2015).

EGAN was founded in 2005 as a non-profit organization in Brussels only with voluntary staff (Hernberg-Sthal and Reljanovic, 2013). EGAN's membership consists of national/regional alliances in Germany, Eastern-Europe, Italy, Netherlands, United Kingdom and Ireland, and of European disease-specific patient organizations with an interest in genetics, genomics and biotechnology. Moreover EGAN maintains many contacts with groups of parent/patient organizations in other countries including Sweden, Spain, Italy, Greece and Balkan countries (EGAN, 2015).

EGAN works in a variety of fields of interest (EGAN, 2015):

- human genetics: information and services
- reproduction: peri-conception, prenatal and neonatal care, information and prevention

- databanking, patient registries and biobanking
- biomedical research
- (advanced) therapy development: gene therapy, cel and tissue therapy
- omics: genomics, nutrigenomics, metabolomics
- animal research and experimentation
- clinical research
- patient participation in research and development
- European health policy

Currently, EGAN participates in European projects including Global Research in Pediatrics (GRIP), the Genetic and Epigenetic Networks cognitive Dysfunction (GENCODYS) and the Preparing for Life Initiative (EGAN, 2015).

3.3 American Organizations and Networks

3.3.1 Genetic Alliance

The history of Genetic Alliance begins with the Orphan Drug Act approval in 1983: **Mid-Atlantic Regional Human Genetics Network (MARHGN)** held a symposium entitled *Genetic Disorders and Birth Defects in Families and Society: Toward Interdisciplinary Understanding*. But it was only 3 years later that Joan O. Weiss founded in Washington DC the Genetic Alliance (Genetic Alliance, 2013).

Nowadays, Genetic Alliance is the largest US non-profit health advocacy organization, which includes in its network more than 1000 disease-specific advocacy organizations, as well as universities, private companies, government agencies, and public policy organizations (Genetic Alliance, 2013; Hernberg-Sthal and Reljanovic, 2013).

Genetic Alliance wants to improve health through the authentic engagement of communities and individuals to build capacity within the genetics community by creating partnerships between stakeholders, improving information for better decision-making, and facilitating the transfer of basic research into novel health technologies (Genetic Alliance, 2013).

The activity of Genetic Alliance is mainly funded by federal grants (60%: Maternal and Child Health Bureau, MCHB), government contracts (20%: Centers for Disease Control and Prevention, CDC; NIH/National Library of Medicine, NLM; Health Resources and Services

Administration, HRSA) and to a minor degree by fees for service, individual donors and industry support (Genetic Alliance, 2013; Hernberg-Sthal and Reljanovic, 2013).

Genetic Alliance includes the following activities and services (Hernberg-Sthal and Reljanovic, 2013):

- Annual Conference;
- Numerous webinars;
- Creation of entries in WikiGenetics and WikiAdvocacy;
- Participation of the community in the Advocates Partnership Program;
- Maintenance of Disease InfoSearch;
- Searchable database with information on advocacy organizations and disease descriptions;
- Listserv Hosting for advocacy organizations;
- Assistance in establishing disease-specific groups.

Current Genetic Alliance's programs include (Hernberg-Sthal and Reljanovic, 2013):

- Access to Credible Genetics Resources Network: provides access to quality information on Duchenne, Becker Muscular Dystrophy and Fragile X syndrome;
- Consumer Focused Newborn Screening Initiatives: a comprehensive resource on neonatal screening for the public;
- Family Health History Programs: community-created tools for discussing family health history and translate knowledge into healthy choices;
- Congenital Conditions Program: collects evidence-based information and coordinates supportive care for parents whose child received a diagnosis prenatally, at birth, or up to one year after birth;
- Genetics for Early Disease Detection and Intervention to Improve Health Outcomes: initiative for early disease detection using clinical, genetic, and family health history information.
- Since 2003 Genetic Alliance has managed a biobank.

3.3.2 Rare Disease Clinical Research Network (RDCRN)

The RDCRN was created in 2003 by the US NIH and the FDA ORDR which is now a part of the National Center for Advancing Translational Sciences (NCATS). In total, according their

website, over 200 diseases are studied by the 22 research groups of the RDCRN (RDCRN, 2016).

The RDCRN is designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing. Through the RDCRN consortia, physician scientists and their multidisciplinary teams work together with patient advocacy groups to study more than 200 rare diseases at sites across the nation (Hernberg-Sthal and Reljanovic, 2013).

The Research Consortia provide individual websites which contain information for patients and physicians regarding disease information, treatment guidelines, ongoing studies, and contact data for patient registries (RDCRN, 2016).

The RDCRN maintains a listing of ongoing clinical trials, which includes information on the disease under study, study title, recruitment status, a brief study description, eligibility criteria, and contact data or locations of participating hospitals (Hernberg-Sthal and Reljanovic, 2013).

3.4 International Conference for Rare Diseases and Orphan Drugs (ICORD)

The International Conference on Rare Diseases and Orphan Drugs society is an international organization for individuals who are active in the field of rare diseases and orphan drugs, with members from academia, industry, patient organizations, regulatory and health authorities, health professionals, and public policy leaders (Hernberg-Sthal and Reljanovic, 2013).

According to their website, the idea of an ICORD Society was born when representatives of many different stakeholders met at the 1st International Conference on Rare Diseases and Orphan Drugs 2005 in Stockholm. Formation of the ICORD Society was a process where these stakeholders met and discussed ICORDs mission and aims in 2006 and 2007. The ICORD Society was formed on 13 September 2007 in Brussels (ICORD, 2015).

The ICORD mission is to improve the welfare of patients with rare diseases and their families worldwide through better knowledge, research, care, information, education and awareness (ICORD, 2015). The organization intends to promote research, ethics, policies and actions on

rare diseases and orphan products in all regions of the world, to provide a global forum for all stakeholders for effective communication, to enhance international cooperation, and to develop tools to address common issues in rare diseases and orphan products (ICORD, 2015).

One of the initiatives promoted by the European Commission, Health Directorate, DG Research and Innovation, and the US NIH ORDR is the International Rare Diseases Research Consortium (IRDiRC). The goals of the consortium are to deliver by 2020, 200 new therapies for rare diseases and diagnostic tests for the rarest diseases (Hernberg-Sthal and Reljanovic, 2013).

3.5 Patient Organizations in Portugal

The **Aliança Portuguesa de Doenças Raras** was founded on 20 February of 2008 with the main goals the representation of its member associations together Institutions in the area oh Health, Rehabilitation, Social Security and Education, or other national and international entities pursuing the same objectives and the social integration of people with rare diseases. The *Aliança* is a national member of EURORDIS (Aliança Portuguesa de Doenças Raras, 2009).

Raríssimas, National Association of Mental and Rare Disorders, opened Casa dos Marcos, the first Resource Centre for Rare Diseases in Portugal, gathering social and healthcare services and planning to respond in the educational area as well. Casa dos Marcos has both residential services and ambulatory care and is establishing several partnerships, nationally and internationally, developing innovative projects in various domains. In fact, it has a unique model of assistance with a mix offer that includes services under contract with the State (a long-term care unit, a residential unit, an occupational activity center and an autonomous residential unit) and private services (Rodwell and Aymé, 2014).

Chapter 4: Policies and Research Funding

Is no doubt that with the introduction of orphan drug legislation, in USA in 1983, the possibility of providing treatments for rare disease patients became reality. A number of policies have been initiated at the European level to improve cooperation and information for better patient access. Funding has been made available in the EU through the European Framework programs and in the USA through the NIH Therapeutics for Rare and Neglected Diseases (TRND) Program for research in rare diseases (Hernberg-Sthal and Reljanovic, 2013).

4.1 Current Model for Financing Drug Development

The traditional process for developing a new drug or biologic product and bringing is to market has become exceedingly expensive and lengthy - estimated to be more than $1 billion, and to take approximately 10-15 years. Only 8 percent of investigational new drugs entering Phase I clinical trials (Wizemann, Robinson and Giffin, 2009; FasterCures, 2010). In addition, the number of new drug approvals has been slowly declining over the last years (see Figure 9) from 53 new molecular entities approved in 1996, to an average of 28 per year between 1999 and 2005 and to 16 in 2007 (Wizemann, Robinson and Giffin, 2009).

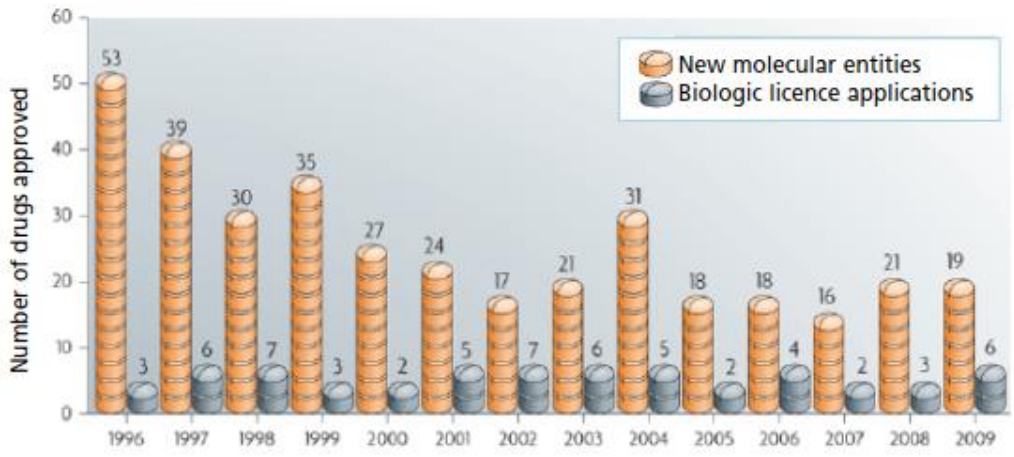


Figure 9 - New Molecular Entities and Biologic License Applications in the EUA. Adapted from (FasterCures, 2010).

FitzGerald in 2008 considered that "both industry and academia are poorly positioned to respond in the current financial landscape. Even considering the potential for blockbuster drugs, this lengthy, high cost, low success rate model is likely to prove unsustainable. For those

far less commercially attractive drugs used to treat rare and neglected diseases, it is simply infeasible (Fitzgerald, 2008). As mentioned, Congress formally recognized the lack of available treatments for rare and neglected diseases and the difficulty of finding companies to develop them. The Orphan Drug Act allows FDA to provide incentives for companies to bring new therapeutic products to market (Seoane-Vazquez *et al.*, 2008; Franco, 2013).

Patient groups, disease foundations, and philanthropic organizations have long recognized that the conventional drug development model is less effective in achieving treatments for orphan diseases, and have therefore devised a range of financial and operational strategies for filing this gap (FasterCures, 2010). As a result, we must to agree that the outlook for the development of drugs for orphan diseases is better today than was two/three decades ago (Wizemann, Robinson and Giffin, 2009).

Of course the riskiest period of drug development and, obviously, the most difficult to fund, is that between basic discovery, generally funded by government, and late-stage development, generally funded by large pharmaceutical companies. This period is often referred to as the "valley of death" (see Figure 10) and includes expensive preclinical tests, pilot manufacturing and early-stage safety and proof of concept efficacy clinical trials (Wizemann, Robinson and Giffin, 2009).

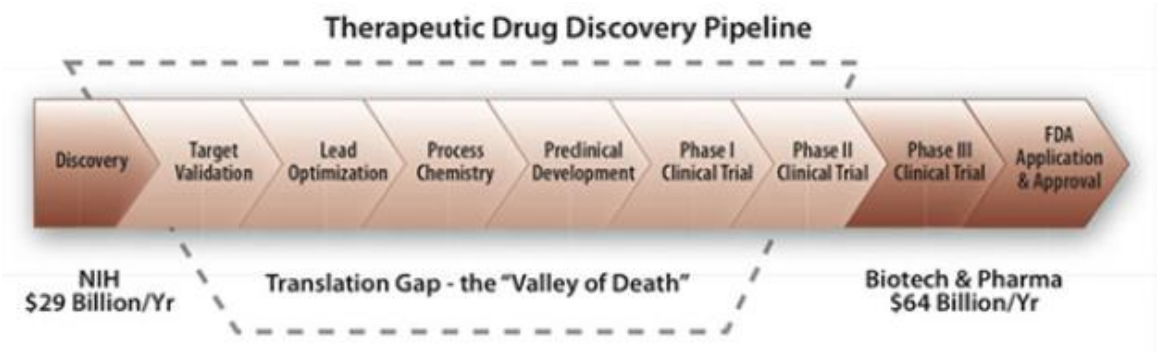


Figure 10 - Map of the Valley of Death. Adapted from (The Michael J. Fox Foundation, 2011)**.**

Because of this, many not-for-profit organizations are advancing to development of drugs for rare and neglected diseases through a broad array of financial and operational strategies aimed at decreasing the risk of investment during this period. There are some examples that is good to know (Wizemann, Robinson and Giffin, 2009):

- Cystic Fibrosis Foundation – has launched entire virtual companies to manage all aspects of the development of new therapies for a single disease: funding, intellectual property, patient registries and clinical trials;
- Muscular Dystrophy Association – aims to advance drug development for 40 neuromuscular diseases primarily through target funding and a process to facilitate access to patients with these diseases.

Such approaches are increasingly relevant to the development of mainstream drugs, which may lead to targeted therapies, for which fewer patients are eligible. An example is trastuzumab (Genentech's Herceptin), a monoclonal antibody therapy for breast cancer – only for HER-2 positive breast cancer (Wizemann, Robinson and Giffin, 2009).

4.1.1 Investors in Drug Development

The principal investors in drug development differ at each stage (Wizemann, Robinson and Giffin, 2009; FasterCures, 2010; Norris *et al.*, 2010; Savaneviciene, Venckuviene and Girdauskiene, 2015):

- **Basic discovery research** – funded primarily by government and philanthropic organizations; In USA, the largest government investments in basic drug discovery research have been made by the National Institutes of Health (NIH). Moreover, in part as a result of the public's impatience with the slow pace of the discovery process, state governments are increasingly taking the initiative in this area: California Institute for Regenerative Medicine provides grants and loans for stem cell research and facilities at California's research institutions and universities; Texas Cancer Initiative, which state funds are dedicated to cancer research conducted in Texas.
- **Late-stage development** – funded mainly by pharmaceutical companies or venture capitalists with some collaborative support from government sources, such as NIH in the USA.

As known, the period between discovery and proof of concept, which means prove the utility of a proposed drug, is considered extremely risky and therefore has been difficult to fund. Several initiatives discussed below have been undertaken to overcome this gap.

4.1.2 Status of Investments

Unfortunately, despite the desire for development of new therapies, several environmental factors negatively affect new investments in drug development. Caskey, in 2008, identified some inhibitors of development (Wizemann, Robinson and Giffin, 2009):

- **Decreased funding for basic research**: fewer investments in basic research can result in fewer new drug therapy candidates, which in turn can result in fewer investments by private industry to advance promising candidates;
- **Regulatory barriers:** Navigating novel products through the existing regulatory pathways is challenging as scientific advances are made and regulations continue to evolve. In the light of the increasing uncertainty of the regulatory process and possible increases in regulatory requirements, investors may shy away from investing in a product before there is clear evidence of its safety and effectiveness.
- **Problems with drug safety:** lawsuits following product withdrawals greatly affect new investments in development. The money spent with this could potentially have funded the development of 30 to 40 new drugs.

4.1.3 Ways to Facilitate Drug Development

After that, it is important to reflect and discuss some suggestions for overcoming the impediments to new drug discovery and development. Table 8 shows some examples of three types of incentives.

Table 8 - Initiatives to facilitate drug development. Adapted from (Wizemann, Robinson and Giffin, 2009)**.**

Academic initiatives	Government initiatives	Private initiatives
- Increase investments in technology that can improve target validation and drug safety	- Government research funding needs to be more focused on forecast morbidity and the cost of care. - FDA and EMA needs to be adequately funded so it can partner with drug developers and direct the research being performed	- Small business innovation research and technology transfer regulations need to be revisited and revised to allow for greater investment; - New incentives for high-risk investors need to be created;

Academic initiatives	Government initiatives	Private initiatives
	toward answering important regulatory questions	- Private disease foundations' provision of support to the academic community for discovery should be embraced; - Experienced investors need to be brought into the innovation process earlier; - The pharmaceutical industry and academia need to work together.

4.1.4 Research Funding in the EU

At the European level, research on rare diseases is being addressed as one of the priority areas in the health field under the EU Framework Programs for Research and Technological Development, which was established in the early 1990s. Sixth Framework Programme for Research (FP6: 2002 – 2006), one of the seven thematic areas supported projects focusing on 'Life sciences, genomics and biotechnology for health'. This thematic area was two-fold, one of the aspects being the fight against major diseases, including rare diseases. E-Rare was a Seventh Framework Programme of the EU funded ERA-Net programme for research on rare diseases (2007-2013). In the first phase of the project (2006-2010) E-Rare launched two Joint Transnational Calls (JTC) (Hernberg-Sthal and Reljanovic, 2013):

- 1st Call – effective collaboration between scientists on a common research project based on complementarities and sharing of expertise;
- 2nd Call – financial input of each partner research funding agency/ministry provided the funding for 16 transnational research consortia with 75 participating research teams from 10 countries for a total research budget of €9.6 million.

At the end of 2010, E-Rare-2 launched its third JTC for proposals: research groups from nine countries were eligible to participate in this call that seeks to promote transnational research collaboration on rare diseases. This initiative allowed for the mobilization of researchers to

tackle the fragmentation of research and the production of new knowledge, encouraging a better coordination of research at the EU level, and fostering dialogue with all stakeholders, including patients (Hernberg-Sthal and Reljanovic, 2013).

Fortunately, rare diseases continue to be a priority in current research programme, **Horizon 2020 (2014-2020)**. Of the current projects, 17 are specifically devoted to support research on the natural history and the pathophysiology of **rare diseases**, and 8 projects cover the pre-clinical and clinical development of **orphan drugs** (European Commission, 2014).

4.1.5 Research Funding in the USA

There are two US institutions responsible for providing and/or administering research funding to stimulate and support the development of orphan drugs in the field of rare diseases: **FDA** and **NIH** (Hernberg-Sthal and Reljanovic, 2013).

4.1.5.1 The FDA Office of Orphan Products Development (OOPD)

The mission of the FDA Office of Orphan Products Development (OOPD) is to advance the evaluation and development of products (drugs, biologics, devices or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. The OOPD evaluates scientific and clinical data submissions from sponsors to identify and designate products as promising for rare diseases and to further advance scientific development of such promising medical products. The OOPD also provides incentives for sponsors to develop products for rare diseases. The programme has successfully enabled the development and marketing of more than 350 drugs and biologic products for rare diseases since 1983 (Hernberg-Sthal and Reljanovic, 2013).

The OOPD administers two extramural grants programme (Hernberg-Sthal and Reljanovic, 2013):

- The **Orphan Products Grants Program** – provides funding for clinical research of drugs, biologics, medical devices and medical foods in rare diseases;
- The **Paediatric Devices Consortia (PDC) Grant Program** – provides funding to develop non-profit consortia to facilitate paediatric medical device development, and this has been the first step in the approval of at least 50 Humanitarian Device Exemption approvals.

The Rare Diseases Program run by FDA aims to facilitate and support the research, development, regulation and approval of drug and biologic product for the treatment of rare disorders. The programme coordinate the development of the CDER policy, procedures and training for the review and approval treatments for rare diseases and work collaboratively with external and internal rare diseases stakeholders to support the development of treatments for rare disorders (Hernberg-Sthal and Reljanovic, 2013).

4.1.5.2 National Institutes of Health (NIH)

The NIH is the US medical research agency. It includes 27 institutes and centers and is a component of the US Department of Health and Human Services. The NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, including investigating the causes, treatments and cures for both common and rare diseases (National Institutes of Health, [s.d.]).

The NIH Therapeutics for Rare and Neglected Diseases (TRND) programme was launched in 2009 and it is a unique programme that creates a drug development pipeline within the NIH and is specifically intended to stimulate research collaborations with academic scientists, non-profit organizations, and pharmaceutical and biotechnology companies working on a rare and neglected illness (Hernberg-Sthal and Reljanovic, 2013). The TRND programme is to be financed directly as part of the National Center for Advancing Translational Sciences' division of pre-clinical innovation. TRND doesn't fund projects directly but helps academic and industry organization access drug development capabilities that include high-throughput screening, medicinal chemistry, and toxicology (Hernberg-Sthal and Reljanovic, 2013).

4.2 Diverse Funding Models

There are multiple approaches to funding the discovery and development of drugs to treat rare and neglected diseases. This dissertation presents four examples of models/approaches to facilitating drug development for rare and neglected diseases (Wizemann, Robinson and Giffin, 2009):

- A not-for-profit pharmaceutical company model;
- A disease foundation that operates a virtual company linking investors with biopharmaceutical companies;
- A for-profit company with a vested interest in rare diseases;

- A global private-equity fund dedicated to advancing drug discovery

4.2.1 Institute for OneWorld Health: A Not-for-profit Pharmaceutical Company

History and structure: OneWorld Health is a small team of pharmaceutical company experts that was launched in 2000 as an experiment, modeled after the pharmaceutical industry but eliminating the profit requirement from the business plan. There is a little venture capital interest in these markets, and start-up activities were deliberately funded primarily through philanthropy. The primary target is neglected disease of the poor resulting from infectious agents or vectors that are not generally prevalent in the developed world (Wizemann, Robinson and Giffin, 2009).

Funding: initial program funding was provided by the Bill and Melinda Gates Foundation. Now has the task of convincing new funders that are worthwhile investments to be made in research and product development addressing neglected diseases (Wizemann, Robinson and Giffin, 2009).

Approach:

- identify promising drug candidates, complete clinical trials, secure local manufacturing and regulatory approval in countries in which target are endemic;
- form partnerships to ensure drug distribution;
- the approach varying depending on the project and remaining flexible, nimble and no bureaucratic. The organization is opportunistic and pragmatic, and adapts as necessary to move a particular technology forward.

Strategies:

- Find new approaches to old diseases;
- Focus on high-risk, high-reward projects;
- Start with parasitic diseases for which there are no vaccines;
- Seek to find new uses for older, off-patent drugs

Portfolio:

- Public health tools for disease elimination programs;
- Consumer products (e.g. antidiarrheal medication);

- Prescription drugs accessed through the formal health care system;
- Active pharmaceutical ingredients - supplier to industry.

4.2.2 Cystic Fibrosis Foundation Therapeutics (CFFT): A Virtual Company for Managing Drug Discovery and Development Alliances

History and structure: Cystic Fibrosis Foundation was established in 1955 by a group of parents of children with cystic fibrosis seeking to ensure that their children would get the best of care. CFFT, established in 2000, is a wholly owned nonprofit drug discovery and development subsidiary of the main foundation (Cystic Fibrosis Foundation, 2015). Its primary mission is to convince biopharmaceutical companies to develop drugs for a disease that affects only 30 000 people in the US and 70 000 worldwide (Wizemann, Robinson and Giffin, 2009).

Funding (Wizemann, Robinson and Giffin, 2009; Cystic Fibrosis Foundation, 2015)**:**

- Funds are provided on a matching basis for preclinical and clinical development;
- Awards are milestones driven;
- A scientific advisory council oversees progress;
- Upon approval of a drug, CFFT receives a multiple of its investment, which it can then reinvest in new products.

Approach: Established business relationships with biotechnology and pharmaceutical companies and works with them to reduce the risk of their investment in cystic fibrosis treatments by providing financial support, access to leading cystic fibrosis experts and research tools, and access to the Cystic Fibrosis Therapeutic Development Network of Cystic Fibrosis Care Centers for facilitation of clinical trials (Wizemann, Robinson and Giffin, 2009; Cystic Fibrosis Foundation, 2015).

Strategies: the primary strategy involves reducing the risk to development partners of entering the cystic fibrosis field and making products more attractive from a business perspective. Keys to success include (Wizemann, Robinson and Giffin, 2009; Cystic Fibrosis Foundation, 2015):

- Understanding the basic defect and the pathophysiology of cystic fibrosis;
- Establishing a business relationship with the partner;
- Providing access to patient populations and information systems to support clinical development.

4.2.3 Genzyme: For-profit Company in the Rare Diseases Arena

History and structure: Genzyme is a biotechnology company founded in 1981. In 1988 it was a small bulk manufacturer of pharmaceuticals and also had a nascent cystic fibrosis research program. With survival of the company as the primary goal, its leadership made a decision to devote all resources to pursuing one therapy for one disease: Gaucher disease. In 1991 Genzyme's first Gaucher treatment, Ceredase, was approved on the basis of a 12-patient pivotal trial. Currently more than 10 000 employees worldwide and annual revenues exceeding $3 billion (Genzyme, 2016).

Approach: Sustainable business for drug development for rare and neglected diseases with 3 basic elements (Wizemann, Robinson and Giffin, 2009; Genzyme, 2016):

- The therapy must be effective and address an unmet medical need, presumably treatment for a disease that causes a life-threatening, severe morbidity;
- There needs to be a global market;
- The price must be sustainable.

4.2.4 Celtic Therapeutics, LLLP: A Private-Equity Model for Addressing Global Health

Structure: a virtual pharmaceutical company comprising a management company that runs a private fund and a biomedical development organization that develops the firm's strategy and manages the outsourcing of all product development components (Wizemann, Robinson and Giffin, 2009).

Approach: acquire and invest in novel therapeutic drug candidates that can address unmet medical need. It buys, licenses, or forms an alliance with a biotechnology company for one of its promising product candidates for an orphan disease that is in phase IIA, develops the product to the point at which a large pharmaceutical partner will be interested, and then sells it at auction to a pharmaceutical company. The model can provide returns to investors following commercial distribution by a pharmaceutical partner, or can help fulfill the mission of a philanthropic organization by facilitating noncommercial distribution through a public-private partnership (Wizemann, Robinson and Giffin, 2009).

4.3 Strategies for Facilitating Sharing of Research Materials and Data

In the biomedical sciences it is essential that research materials and data be shared if progress is to be achieved. This dissertation presents some strategies for leveraging time and resources to meet this crucial need, particularly in case of orphan medicines.

Dr. Mowatt explained that the sharing process is relatively simple: request, negotiate and receive (Wizemann, Robinson and Giffin, 2009). In the following two sub-themas are presented examples of models of sharing data for biomedical research.

4.3.1 The Alzheimer's Disease Neuroimaging Initiative (ADNI): A public-Private Partnership

ADNI was launched in 2002 with four working groups to address magnetic resonance imaging(MRI), positron-emission tomography (PET), study design and biological measures. A goal is to identify biomarkers of disease progression. ADNI is funded through a cooperative agreement at 12$ million per year for 5 years. However total funding exceeds $60 million, with NIH funds, organizations and companies funds and 2 nonprofit organizations. ADNI is truly a public-private partnership. The heart of ADNI is open sharing of data and samples, which includes (Wizemann, Robinson and Giffin, 2009; ADNI, 2013):

- Rapid public access to all row and processed data;
- A central repository for MRI and PET images;
- A clinical database;
- Databases that are in the public domain and available to all qualified investigators;
- No special access privileges (ADNI investigators do not have priority access);
- A data-sharing and publication committee, an ADNI data-use agreement that is a prerequisite for obtaining the data;
- Biological sample sharing.

ADNI data are being utilized worldwide. In the 22 months after the first application for data use was approved, there were more than 270 000 image downloads by 265 investigators and clinical data were downloaded by 203 investigators (Wizemann, Robinson and Giffin, 2009).

4.3.2 Genetic Alliance Biobank

In 1994, Terry's children were diagnosed with a rare disease – pseudoxanthoma elasticum (PXE). Terry and her husband took action by founding PXE International and the PXE International Blood and Tissue Bank. They served as a the model for the Genetic Alliance Biobank, founded in 2003 (Genetic Alliance Biobank, [s.d.]; Wizemann, Robinson and Giffin, 2009).

The vision of the Genetic Alliance Biobank is to revolutionize access to the information and resources needed to enable the translation of research into diagnostics, drugs and services that support individualized decision making. Genetic Alliance seeks to address the needs by providing (Genetic Alliance Biobank, [s.d.]; Wizemann, Robinson and Giffin, 2009):

- Access to well-annotated samples;
- The ability to obtain consent and reconsent from study participants;
- Longitudinal clinical data collection;
- A clinical health information registry;
- Medical record collection and interoperability with electronical medical records;
- Archival exchange with the database of Genotype and Phenotype, which is part of the NIH system.

The primary interest of Genetic Alliance constituents is to ensure that the experimental treatments used in the clinical trials are effective (Wizemann, Robinson and Giffin, 2009).

These two good examples sharing of materials and data on rare diseases, should now begin to be applied in the investigation into neglected diseases where resources are even scarcer and there are fewer companies interested in developing therapeutic products.

The new models for funding research and sharing materials and data discussed previously necessitate newer and more effective strategies for addressing issues of intellectual property.

4.4 Strategies for Navigating Intellectual Property

The ownership and sharing of knowledge play an important role in scientific innovation, drug development and the creation of affordable access to health technologies. Establishing intellectual property rights protects proprietary interests so that sufficient financial incentive exists to fuel innovation (Mimura, 2007). However, by definition, drugs for orphan diseases

serve small or resource-limited markets, and market exclusivity may be less lucrative. It is important to discuss how creative management of intellectual property rights can serve both public and private interests relative to rare diseases of industrialized countries and neglected diseases endemic to developing countries.

The typical market life cycle of a drug begins with a period of sunken research and development (R&D) investment, followed by a period of return on investment after the drug enters the market. The return on investment diminishes as competing products enter the market and is exacerbated when generic competition begins upon expiration of the patent period.

The system of innovation in US is driven largely by intellectual property. To protecting proprietary knowledge that might hold off competition, intellectual property rights impact the affordability of patented end products, even when there has been significant public funding of their development. To address the latter problem, a variety of largely public and philanthropic funding models of financing mechanisms have evolved (Mueller-Langer, 2013):

- **Push mechanisms** – paying for inputs into the research process. The usual push solutions have included NIH and other research grants, as well as R&D tax credits. Another example is licensing a drug to an entity that can produce it at reduced cost, such as a company in the developing world, rather than to a large private-sector company (Figure 11).
- **Pull mechanisms** – work to play for the outputs of R&D processes. One model is advanced market commitments that guarantee revenue return, such as those for vaccines for developing countries. Other example involve prizes and patents buyouts. In exchange for the prize awarded, the intellectual property might be licensed for generic production, which could create competition among multiple firms, or it could be adapted by others for better targeted use in developing countries (Figure 11).

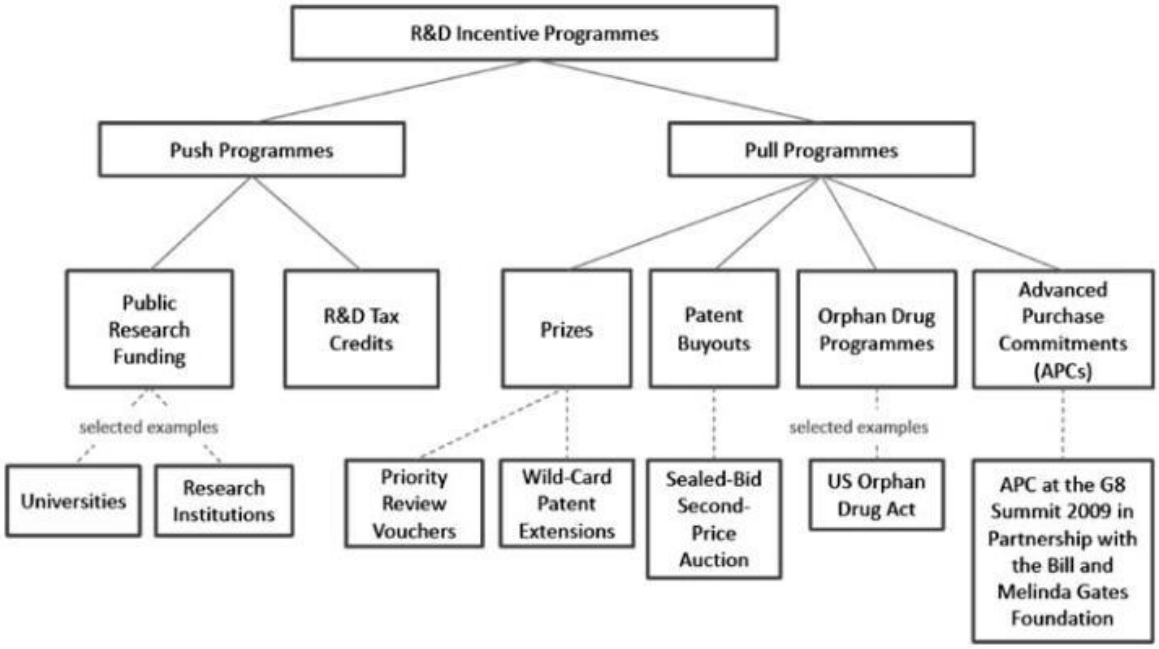


Figure 11 - Push and pull R&D incentive programs and selected examples (Mueller-Langer, 2013)**.**

For orphan diseases there is too often a reliance on dual markets, whereby a higher-paying or sufficiently large market allows for a second market segment in which a product might be priced more affordably. The product might be produced because of sufficient economies of scale in the first market, or the patent license might be treated differently, perhaps royalty-free, in the second market (Wizemann, Robinson and Giffin, 2009). I present three examples of serendipitous dual markets (Table 9).

Table 9 - Examples of three Serendipitous Dual Markets (Wizemann, Robinson and Giffin, 2009).

	Product/Tech-nology	Partners	Dual-product markets	Intellectual Property Approach
Dual market pricing: **ASAQ**	A new fixed-dose combination of artesunate and amodiaquine (ASAQ) to treat malaria in sub-Saharan Africa	Drugs for Neglected Diseases initiative (DNDi) and Sanofi Aventis	Public market: once a day dosing, no-profit/no-loss price to public organizations in endemic countries <$1 for full treatment; Private market: under the brand name Coarsucam, $3-4 for full treatment	The product was not patented. DNDi receives a percentage of the revenues from the sales of Coarsucam, which it uses toward lowering the preferential price of ASAQ in the public market.
Dual markets for a product: **Eflornithine**	Eflornithine	Bristol-Meyers Squibb (BMS)/Gillette and Aventis Pharma	Public market: treatment of African sleeping sickness; Private market: under the name Vaniqa, a cream for slowing the growth of unwanted facial hair in women	BMS and Gillette market Vaniqa under a license from Aventis Pharma. BMS funds the bulk material costs for producing 60,000 vials of eflornithine.
Dual markets for licensing: **Global Vaccines, inc.**	Novel vaccines technologies	Global Vaccines, Inc (GVI) and the University of North California (UNC)	Public market: non-commercial vaccine markets and/or orphan vaccines; Private market: commercial vaccine markets and/or nonvaccine applications	GVI secured a license from UNC for royalty-free application and use of its vaccine technology in non-commercial or orphan vaccine markets.

Chapter 5: Clinical Trials for Orphan Drugs

Clinical phase orphan drug development typically starts with an orphan drug designation (ODD). In most cases, at an early stage, scientific advice meetings regarding protocol assistance or pre-submission meetings are held with the EMA or FDA. In the EU, scientific advice for assisting in protocol development of orphan drugs is free of charge for SMEs (EMA 663496/2012).

As with other drug development for human use, product development of orphan drugs proceeds stepwise and in four phases during clinical development: after the discovery phase (target, therapeutics), non-clinical safety testing (animal and *in vitro* studies) and process development for manufacturing of large-scale batches, regulatory authorities may approve entry into the human phase (Field and Boat, 2010; Hernberg-Sthal and Reljanovic, 2013). The diagram bellow shows some key features of clinical trials phases (Figure 12):

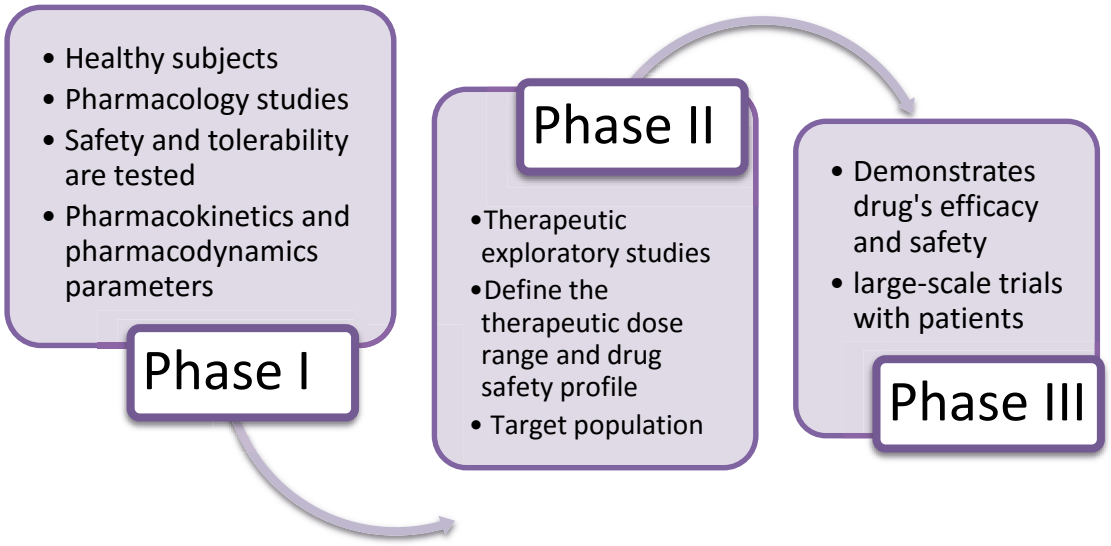


Figure 12 - Clinical Development Phases. Adapted from (Field and Boat, 2010).

Sometimes, exploratory human studies (Phase 0) are conducted in the development of drugs for serious or life-threatening diseases at entry into the human phase, which may investigate absorption of microdoses and involve fewer resources to make Go/No Go decisions during substance selection (Hernberg-Sthal and Reljanovic, 2013).

Nevertheless, after approval, further safety data will be collected in observational studies (Phase IV) in unselected patients under clinical practice conditions or from spontaneous reporting of adverse drug reactions (Hernberg-Sthal and Reljanovic, 2013).

After this brief review of concepts about clinical trials is important to think about the obstacles/challenges in conducting clinical tests with orphan drugs. Some of these are the following (Buckley, 2008; Hernberg-Sthal and Reljanovic, 2013):

- Complex logistical issues (few and disseminated patients around the world);
- Ethical issues (use of placebo, research in vulnerable populations including mentally impaired and children);
- Disease heterogeneity in manifestation and fluctuation of severity;
- Limited knowledge of disease natural history;
- Lack of accepted clinical efficacy outcome measures;
- No established minimum clinically important difference;
- Validation of biomarkers;
- Absence of animal models for diseases.

5.1 Strategies for Facilitating Clinical Trials: Regulatory tools

From the regulatory/legislative perspective, there are special challenges associated with Food and Drug Administration review and approval of products to treat rare diseases. The majority of New Drug Applications (NDAs) for orphan drugs are based on small clinical trials, some with as few as 20 patients. Marketing approval for all drugs requires, by law, "substantial evidence of effectiveness". But exactly how that evidence is provided is negotiable, and communication with FDA can help ensure the most effective use of the sponsor's limited financial and human resources (Wizemann, Robinson and Giffin, 2009; Field and Boat, 2010).

The Orphan Drug Act has been successfully implemented, resulting in the approval of 326 products to treat orphan drugs over the past 25 years. There are additional tools pertaining to the regulation of nonorphan drugs, such as the Prescription Drug User Fee Act (PDUFA) and the FDA Modernization Act of 1997 (FDAMA), that can also help advance the development of orphan products (Wizemann, Robinson and Giffin, 2009; Field and Boat, 2010):

- **Fast-track designation** – can be given to a drug product that is both intended to treat a serious/life-threatening condition and claimed to address an unmet medical need. This allows more involvement with FDA through schedule meetings and permit rolling review, whereby the NDA can be submitted in sections.

- **Accelerated approval** – is based on a surrogate endpoint rather than a clinical outcome. Proof of a clinically meaningful benefit, which can take a long time, is not required at the accelerated approval, and verification studies are conducted post-approval.
- **Priority review** – can be request at the time a sponsor submits a marketing application and if granted, commits FDA to a PDUFA goal date of 6 months, rather than standard 10 months review cycle.
- **Communications with FDA** – There are a variety of opportunities for communication with FDA such formal meetings, special protocol assessments and informal meetings. The Table 10 explain the key features of these types of communication.

Table 10 - Opportunities to communicate with FDA(Wizemann, Robinson and Giffin, 2009).

Communications with FDA	
Formal Meetings	**Type A -** necessary for an otherwise stalled product development program to proceed or to address an important safety issue; within 30 days of FDA's receipt of sponsor request for meeting. **Type B –** held at specified clinical stages or milestones: pre-IND, end of phase II, Pre-NDA/BLA; within 60 days of FDA's receipt of sponsor request for meeting. **Type C –** Any meeting that is not type A or B; within 75 days of FDA's receipt of sponsor request for meeting.
Special Protocol Assessments	FDA's evaluation of the adequacy of protocol's design, conduct, and analysis relative to regulatory requirements for approval FDA response issued within 45 days
Informal Meetings	Usually response to a limited number of specific questions that may require only yes/no answers, or brief clarifications of previous responses.

In the EU an **accelerated evaluation** might be initiated by the CHMP in exceptional cases when a medicinal product is intended to provide an answer to a major public health need, defined by three cumulative criteria:

- The seriousness of the disease to be treated (e.g. heavily disabling or life-threatening);
- The absence of an appropriate alternative therapeutic approach, and
- The anticipation of exceptional high therapeutic benefit.

According EMA's website, the European Medicines Agency (EMA) is developing a scheme for priority medicines (PRIME), to optimize the development and **accelerated assessment** of medicines of major public health interest. The scheme is based on enhanced interaction and early dialogue with medicine developers. EMA expects to launch PRIME in the first quarter of 2016 (EMA, 2015).

PRIME will provide enhanced scientific and regulatory support to companies developing medicines that may offer new therapeutic options to patients who currently have no treatment options, or a major therapeutic advantage over existing treatments. EMA considers these priority medicines (EMA, 2015). Through the scheme, EMA aims to:

- Optimize the development and facilitate the accelerated assessment of new priority medicines to benefit patients as early as possible;
- Encourage medicine developers to focus on medicines with a potential significant benefit.

EMA foresees the eligibility criteria for PRIME to be those of the accelerated assessment procedure. This means that to be eligible to enter the scheme, a medicine would have to show preliminary clinical evidence indicating that it has the potential to bring significant benefits to patients with unmet medical needs and hence be of major interest from a public health and therapeutic innovation perspective (EMA, 2015).

EMA proposes earlier entry into the scheme for micro-, small- and medium-sized enterprises (SMEs) and applicants from the academic sector on the basis of compelling non-clinical data and tolerability data in initial clinical trials. This aims to provide further support to

these sponsors who are known to play a key role in the development of innovative medicines and may benefit even more from PRIME support (EMA, 2015).

Medicines might receive approval in the EU under any three different headings (Buckley, 2008):

- **Normal approval**
- **Approval under exceptional circumstances** – might be given when comprehensive data cannot be provided, for instance because of the rarity of the disease or because of ethical barriers. Such an approval is granted on the basis of specific obligations of the license holder to inform the regulator about safety and efficacy with the passage of time;
- **Conditional approval** – legal for one year, renewable, when the dataset submitted is incomplete, but there is a positive risk-benefit balance evident from that available as long as the license holder provides comprehensive clinical data after approval.

5.2 Designing Robust Clinical Trials for Orphan Drugs

In contrast to the USA, a dedicated EU Guideline (CHMP/EWP/83561/2005) exists on clinical trials in small populations. In addition, several other EU regulatory documents govern further details specific to the development of orphan products:

- 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 (ENTR/6283/00 Rev 3);
- Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009);
- Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation (EMA/COMP/436/01);
- Regulation of the European Parliament and of the Council on medicinal products for paediatric use (EC 1901/2006).

5.2.1 Review of Hurdless

As I said before, in the beginning of this chapter, one of the most obvious obstacle for conducting clinical studies in rare diseases is the lack of affected patients. They may be scattered worldwide or clustered in a specific geographic area. Thus, enrolling a large patient

cohort for a clinical trial is inherently demanding or may not be practical. In fact, some orphan medicines were approved without any formal trials: betaine for homocystinuria was approved in the EU on the basis of 202 spontaneous literature reports and hydroxycarbamide for sickle cell disease on the basis of bibliographic data and registries (Hernberg-Sthal and Reljanovic, 2013).

Despite de constraints and many challenges, no methods exist that are relevant to small studies that are not also applicable to large studies. Although, other supporting evidence, like published literature, compassionate use information, existing approvals in other ICH regions), was sometimes included and clinical evidence may be derived from a single study (Table 11).

Table 11 - CDER Orphan approvals in 2010.Adapted from(Hernberg-Sthal and Reljanovic, 2013)**.**

Product	Indication	Type	Exposure	Pivotal	Design	Primary Endpoint
Velaglucerase (VPRIV®)	Gaucher Disease	NDA	n=99	1 study (n=25)	RND, DB	Mean change of hemoglobin between low-dose and high-dose groups
Carglumic acid (Carbaglu®)	N-acetylglutamate synthase deficiency	NDA	n=23	1 case series	OL, Hx controlled	Time course of plasma ammonia concentration.
Alglucosidase (Lumizyme®)	Late-onset Pompe Disease	BLA	Supportive evidence from post-marketing registry of infantile-onset form (n=15)	1 study (n=90)	RND, DB, PC	Difference between treatments groups in mean forced vital capacity and mean 6-min walk test.

RND: randomized; DB: double-blind; OL: open-label; Hx: historical; PC: Placebo controlled

Less conventional and/or less commonly seen methodological approaches are therefore sometimes needed and may be acceptable if they help to improve the interpretability of the study results. There is no single best strategy for successful clinical development of orphan medicines (Hernberg-Sthal and Reljanovic, 2013).

Frequently the number of patients with a specific rare disease is not only small, but the study population must be collected worldwide, which adds to the complexity and costs of rare diseases trials. During the development of Myozyme® by Genzyme, patient of 39 study participants at eight sites in five countries did not have to relocate. This includes bringing patients and their families to other continents, foreign cultures or adversarial political systems. Parents had to quit jobs; families needed housing for several months, assistance with travel, funding, interpreters, immigration support; and children had to attend new schools. Moreover, it must be kept in mind when conducting clinical trials with rare diseases patients that they belong to an especially vulnerable population of research subjects (Hernberg-Sthal and Reljanovic, 2013).

In contrast to conventional drug development programs, which include the paediatric population late in development when sufficient human safety experience is available from adult trials, infants may be the first subjects exposed to orphan drugs, such as in the case of Myozyme®. They need limited pilot plant capacity, are frequently in an early disease stage without complications, exhibit larger effect size to treatment, and may be the patient population with the highest benefit from therapy (Hernberg-Sthal and Reljanovic, 2013).

The selected sample of study population must be a representative sample of the entire population affected by the disease under investigation in order to ensure external validity of the study. **External validity** may be checked by analysis of data in screening logs by demonstration that enrolled and excluded patients are not different (Hernberg-Sthal and Reljanovic, 2013).

The degree of evidence provided as the basis of approval may vary between orphan drugs applications. The guideline on clinical trials in small populations (CHMP/EWP/83561/2005) provides as hierarchy of study designs:

Internal validity is achieved by a control group. The type of control determines the level of evidence that may be gained from a clinical study. Controlled studies with low statistical power of an important treatment effect may be preferable to no controlled studies. Conducting a randomized controlled trial should be attempt but is not always feasible with orphan drug development (Hernberg-Sthal and Reljanovic, 2013).

The use of **placebo** is subject to ongoing debate in light of the current version of the Helsinki Declaration. Nevertheless, the use of a placebo is considered acceptable by most researchers if the patient will not be harmed by deferral of effective treatment or when no therapy is available or lack of benefit to patients is negligible. Generally, it may be not be justifiable to conduct placebo-controlled studies in a later stage when results of first uncontrolled, open-label studies have been obtained (Hernberg-Sthal and Reljanovic, 2013).

Internal control of a study may also be achieved in a crossover trial with a patient assigned to both treatments in random order, thus serving as its own control. The advantage is lower patient numbers compared with a parallel group trial and a higher patient acceptance as maximum exposure to inactive placebo is only 50%. The design is suitable for short trials with rapid response as long-term fluctuations in the course of the disease would not occur within the study period. However, the design is limited to diseases that have comparable severity at the beginning of both periods and to drugs with a half-life that permits wash-out in a couple of days to avoid carry-over (Hernberg-Sthal and Reljanovic, 2013).

Obviously, if an established treatment is available, a trial with this drug as an active comparator, either blinded or unblended, may be conducted to internally control of the study. In order to conduct a trial using a historical control group (untreated patients or available standard therapy), the disease must be well differentiated, with steady and rapid progress and be free of additional interventions during the study period. Conducting a trial using historical controls may actually take longer, because endpoints must be controlled against what is historically known about the effectiveness of the product. In fact, patient registries may be used as a source for historical controls. However, frequently, there are no published data of sufficient quality available on a specific disease and patients have to be followed in a natural history study to obtain this information (Hernberg-Sthal and Reljanovic, 2013).

Table 12 shows the positive and negative impacts on the clinical development strategy according the existence or absence of previously approved product:

Table 12 - Advantages and Disadvantages of existence or absence of a previously approved product.

Approved Therapy exist	Without approved therapy
Advantages:	**Advantages:**
Boarder knowledge of the disease Study endpoints established Experienced study sites Better diagnostic tools, epidemiology data and disease classification	More patients may be willing to enter a study; Investigators may probably be more enthusiastic The upcoming availability of a potential treatment must be efficiently communicated to small patient communities living disseminated over the world.
Disadvantages:	**Disadvantages:**
The number of patients willing to test a new medicine with unproven effectiveness will probably lower Superiority over the existing treatment must be established	Established outcomes measures not exist Knowledge on natural disease history can be scarce Placebo use and availability of the treatment after the study will pose ethical problems

5.2.2 Study Endpoints

A carefully selected study question is the starting point for developing a feasible design. The basis for it is some basic information regarding which symptoms will be targeted by the new treatment, how they appear (progressive, periodic, sporadic), what treatment duration is necessary to see clinical change in a certain disease, and how treatment effects may be quantified.

A study endpoint, consists of an outcome parameter that can be measured. They can be classifying into "**direct" endpoints** or **surrogate endpoints**. The following table is intended to present the characteristics of both (Katz, 2004; Aronson, 2005).

Table 13 - Key Characteristics of "Direct" Endpoints and Surrogate Endpoints. Adapted from (Katz, 2004; Aronson, 2005; Fleming and Powers, 2013)**.**

"Direct" Endpoints	Surrogate Endpoints
Clinically meaningful endpoints that directly measure how a patient feels, functions or survives; Represent or characterize the clinical outcome of interest: **Objective** – survival, disease exacerbation, clinical event, etc. **Subjective** – symptom score, health related quality of life, etc. The basis for approval of new drugs.	Laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint; Ideally, the surrogate should exist within the therapeutic pathway between the drug and meaningful benefit; Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint. Considered acceptable in life-threatening conditions as a higher risk associated with treatment is tolerated.

The choice of the primary endpoint may pose considerable problems. In some cases, the 'most appropriate' clinical endpoint may not be known or widely agreed or a validated clinical endpoint may not exist. In other cases, the mode of action of the test treatment may not be

well enough known to predict which of several possible outcomes will be affected (Katz, 2004; Fleming and Powers, 2013).

In rare diseases studies, it may sometimes not be possible to pre-specify the primary clinical endpoint, and collecting data on various sensible endpoints should be attempted (CHMP/EWP/83561/2005). Moreover, for a given clinical endpoint or validated surrogate endpoint recruitment of a sufficient number of patients would be difficult or demonstration of this endpoint would take an unreasonable length of time. Then use of other **surrogate markers** as substitutes for a clinical endpoint may be considered. The term 'surrogate endpoint' should only be used for biomarkers, which have been validated. However, selection of a surrogate marker as study endpoint requires it to be reasonably likely – based on epidemiologic, pathophysiologic, or other evidence – to predict benefit. Prediction in itself may not be sufficient to establish efficacy. Considerations should include (European Medicine Agency, 2006):

- How closely changes in the surrogate endpoint are causally linked to changes in a clinical endpoint or symptom;
- How much risk is associated with the therapy;
- What other therapies (if any) are available for the same condition.

Biochemical markers, imaging parameters and pathologic endpoints have been used as surrogate endpoints for the approval of orphan drugs. However, starting in the research phase, the understanding of a specific rare disease is frequently incomplete. It can limit entry into the clinical phase, for example by absence of biomarkers that describe the course of the disease and allow measuring of response to potential treatments. In addition, sometimes there are no established animal models and generation of knock-out and transgenic animal requires adequate facilities and expert knowledge (Katz, 2004; Fleming and Powers, 2013).

Traditionally, biomarkers are used to evaluate short-range responsiveness to characterize the dose range in pharmacodynamics studies or proof-of-concept clinical studies. They reflect biological response but not necessarily clinical efficacy. They can provide a linkage between the drug's mode of action and the molecular basis of disease. The link to the disease must be established in a validation step that shows that they are specific, reproducible and have prognostic value. The validation step is not trivial and may not be achieved with small groups, such as is rare diseases (Aronson, 2005; Fleming and Powers, 2013).

5.2.3 Adaptive Study Designs

Studies should be conducted with sufficient participants to ensure adequate power for answering the research question. However, if this is not possible, small clinical trials may still provide a valuable piece of evidence regarding the efficacy of interventions. Small clinical trials are those that, irrespective of the absolute number, are insufficient to definitely answer a scientific problem. They may be conducted in a small population such as in the case of rare diseases, emergency situations or by budget constraints. Small clinical trials are more prone to variability and may only be adequately powered to detect large intervention effects (Hernberg-Sthal and Reljanovic, 2013).

An adequate planning is crucial especially if non-standard designs are used. But whenever possible, standard statistical methods and trial design should be applied as well in the development of orphan drugs in order to avoid problems with regulatory acceptance in the application for marketing approval (Hernberg-Sthal and Reljanovic, 2013).

The randomized, parallel-group controlled clinical trial design is generally considered as the gold standard, but in some situations it is difficult to use this design. The minimization of systematic bias remains fundamental, as for the more classical trial designs. These biases include (Cornu *et al.*, 2013):

- **Selection bias** which is the biased allocation of patients to treatment or placebo groups;
- **Performance bias** which is the unequal provision of care apart from the treatment under evaluation;
- **Detection bias**, which is the biased assessment of the outcome;
- **Attrition bias** which is the biased occurrence and handling of deviations from protocol and loss-to-follow-up.

With orphan medicines, most frequently the necessary sample size to conduct a clinical study with parallel groups of patients may not be accrued with the small number of available patients suffering from a specific disease and alternative trial designs may be used (Buckley, 2008; Hernberg-Sthal and Reljanovic, 2013).

Crossover trials

It is a traditional design but may be useful in cases of small clinical trials and therefore its features will be presented here. Each subject serves as their own control (Figure 13); May be used in the following situations (Wellek and Blettner, 2012):

- Chronic (relatively stable) diseases are under study;
- Prophylactic drugs with relatively short half-life are being investigated;
- Relatively short treatment periods are considered;
- Baseline and washout periods are feasible.

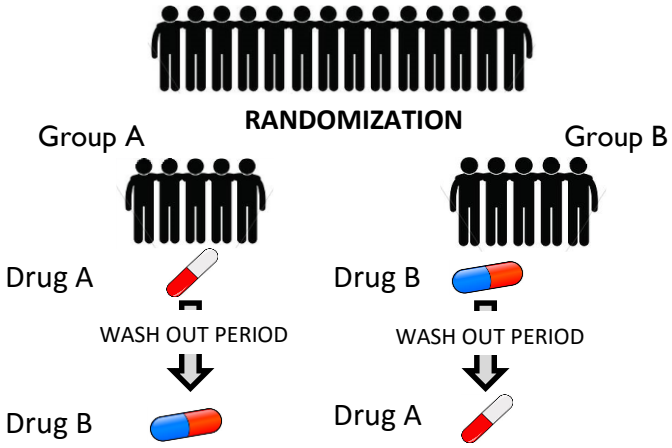


Figure 13 - Crossover trial design

Advantages (Wellek and Blettner, 2012):

- It allows a within-patient comparison between treatments, since each patient serves as his or her own control. Thus, half or considerably fewer subjects will be needed compared with a parallel group study;
- It removes the interpatient variability from the comparison between treatments.
- With a proper randomization of patients to the treatment sequences, it provides the best unbiased estimates for the differences between treatments.

Disadvantages (Wellek and Blettner, 2012):

- Carry-over effects: the residual influence of treatments on subsequent treatment periods. Avoided by wash out period.
- Order effects: Order in which they are administered affects the outcome.
- Period effects: The difference between the study periods.
- Drop-outs can be higher.

N-of-1 designs

They are cross over trials in which one participant receives the experimental and the control interventions, in random order (Figure 14). Typically the number of pair of interventions varies from two to seven. The number of interventions is not pre specified so that the clinician and the patient can decide to stop at will. Many limitations of crossover studies apply to this design as well. They may be useful when (Lillie *et al.*, 2012):

- An RCT has shown that some patients are unresponsive to treatment.
- If there is doubt about whether a treatment is really providing benefit to the patient.

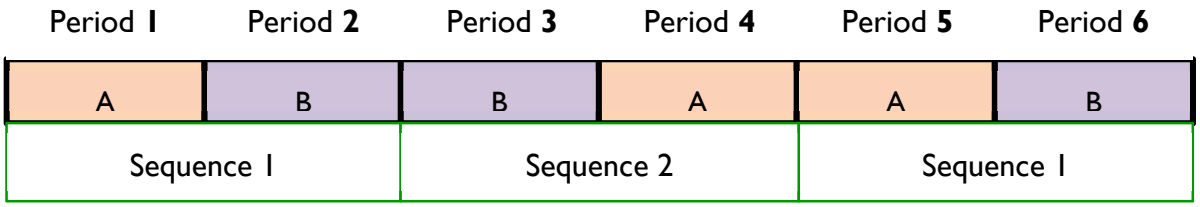


Figure 14 - Schematic representation of N-of-1 Design. Adapted from(Lillie *et al.*, 2012)**.**

Adaptive Designs

In 2004, FDA kicked off a *Critical Path Initiative* to assist the sponsors in identifying the scientific challenges underlying the medical product pipeline problems. In 2006, the FDA released a *Critical Path Opportunities List* that calls for advancing innovative trial designs. This document interprets it as the encouragement for the use of innovative **adaptive design methods** in

clinical trials and the potential use of Bayesian approach in clinical research and development (Chow and Chang, 2008; Mahajan and Gupta, 2010).

According FDA, an adaptive design clinical trial as "a design that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study" (FDA, 2010).

Adaptations that are commonly employed in clinical trials can be classified into three categories: prospective adaptation, concurrent (or ad hoc) adaptation and retrospective adaptation (Table 14).

Table 14 - Classification of adaptations in clinical trials.(Mahajan and Gupta, 2010)

Type of adaptations		
Prospective adaptations (design adaptation)	**Concurrent (or had oc) adaptations**	**Retrospective adaptation**
Adaptive randomization Stopping a trial early due to safety futility or efficacy at interim analysis Dropping-the-losers Sample-size re-estimation	Modifications in inclusion/exclusion criteria Evaluability criteria Dose/regimen and treatment duration Changes in hypotheses and/or study endpoints	Modifications and/or changes made to statistical analysis plan prior to database lock or unblinding of treatment codes.

Although, flexibility does not mean that the trial can be modified any time at will: the modification and adaptations have to be pre-planned and should be based on data collected from the study itself. An adaptation is referred to a change made to the trial procedure and/or statistical procedure during the conduct of a clinical trial (Chow and Chang, 2008). (Figure 15)

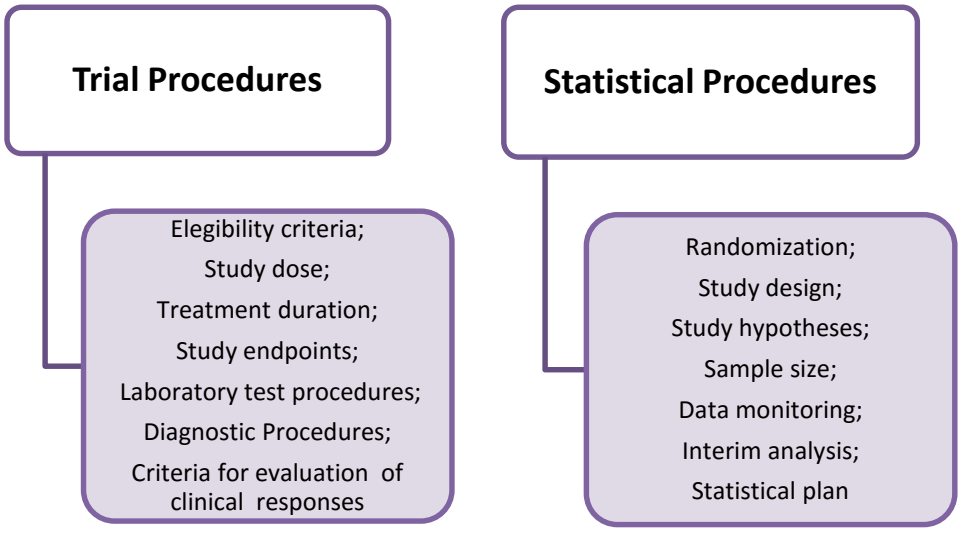


Figure 15 - Examples of possible adaptations in an adaptive design (Chow and Chang, 2008).

Group-sequential methods

A group sequential design is a design that allows for prematurely stopping a trial due to safety, futility/efficacy or both with options of additional adaptations based on results of interim analysis. Various stopping boundaries based on different boundary functions for controlling an overall type I error rate are available in the literature (Chow and Chang, 2008).

The most familiar example is the 3+3 phase I trial design for finding a maximum-tolerated-dose. In a 3+3 trial design, three patients start at a given dose and, if no dose-limiting toxic effects are seen, three more patients are added to the trial at a higher dose. If there is one instance of limiting toxicity in the first group, three more patients are added at the same dose. If two (or all three) in any cohort show dose-limiting toxicity, the next lower dose is declared to be the maximum tolerated (Mahajan and Gupta, 2010).

Response-adaptive designs: play-the winner/drop-the-loser

These methods shift the allocation to treatment (from 1:1) to the more effective intervention ('play-the-winner') before the next patients will be included. Thus outcome data must be available quickly, which is not possible very often with clinical outcomes, but is sometimes available with the use of biomarkers (Mahajan and Gupta, 2010).

A **drop-the-losers** design is useful in phase II clinical development especially when there are uncertainties regarding the dose levels. Typically, drop-the-loser design is a two-stage design: at the end of the first stage, the inferior arms will be dropped based on some pre-specified criteria. The winners will then proceed to the next stage. In practice, the study is often powered for achieving a desired power at the end of the second stage (or at the end of the study). In other words, there may not be any statistical power for the analysis at the end of the first stage for dropping the losers (or picking up the winners) (Mahajan and Gupta, 2010).

Adaptive dose-finding design

An adaptive dose finding (e.g., escalation) design is often used in early phase clinical development to identify the minimum effective dose (MED) and/or the maximum tolerable dose (MTD), which is used to determine the dose level for the next phase clinical trials (Chow and Chang, 2008). For the adaptive dose-finding design, the method of Continuous Re-Assessment Method (CRM) in conjunction with the Bayesian approach is usually considered. The Bayesian approach was developed specifically to deal with new data as they come in and to update the probabilities under investigation (Mahajan and Gupta, 2010).

Biomarker Adaptive Design

This design allows for adaptations based on the response of biomarkers such as genomic markers. Involves biomarker qualification and standard, optimal screening design, and model selection and validation. It should be noted that there is a gap between identifying biomarkers that associated with clinical outcomes and establishing a predictive model between relevant biomarkers and clinical outcomes in clinical development. A prognostic biomarker informs the clinical outcomes, independent of treatment. A predictive biomarker informs the treatment effect on the clinical endpoint (Chow and Chang, 2008; Mahajan and Gupta, 2010).

A biomarker-adaptive design can be used to: select right patient population; identify nature course of the disease; early detection of disease and help in developing personalized medicine (Chow and Chang, 2008).

Adaptive Treatment-Switching Design

Design that allows the investigator to switch a patient's treatment from an initial assignment to an alternative treatment if there is evidence of lack of efficacy or safety of the initial treatment (Chow and Chang, 2008; Mahajan and Gupta, 2010).

Adaptive-hypotheses design

Adaptive-hypotheses design refers to a design that allows modifications or changes in hypotheses based on interim analysis results. This method often considered before database lock/or prior to data unblinding. Some examples include the switch from a superiority hypothesis to a non-inferiority hypothesis and the switch between the primary study endpoint and the secondary endpoints (Chow and Chang, 2008; Mahajan and Gupta, 2010).

Adaptive seamless phase II/III design

A program that address within single trial objectives that are normally achieved through separate trials in phase IIb and phase III of clinical development. Is an adaptive seamless phase II/III trial design that would use data from patients enrolled before and after the adaptation in the final analysis. This method consists in a two-stage design (Figure 16) of a so-called learning stage (phase IIb) and a confirmatory stage (phase III). A typical approach is to power the study for the phase III confirmatory phase and obtain valuable information with certain assurance using confidence interval approach at the phase II learning stage (Mahajan and Gupta, 2010).

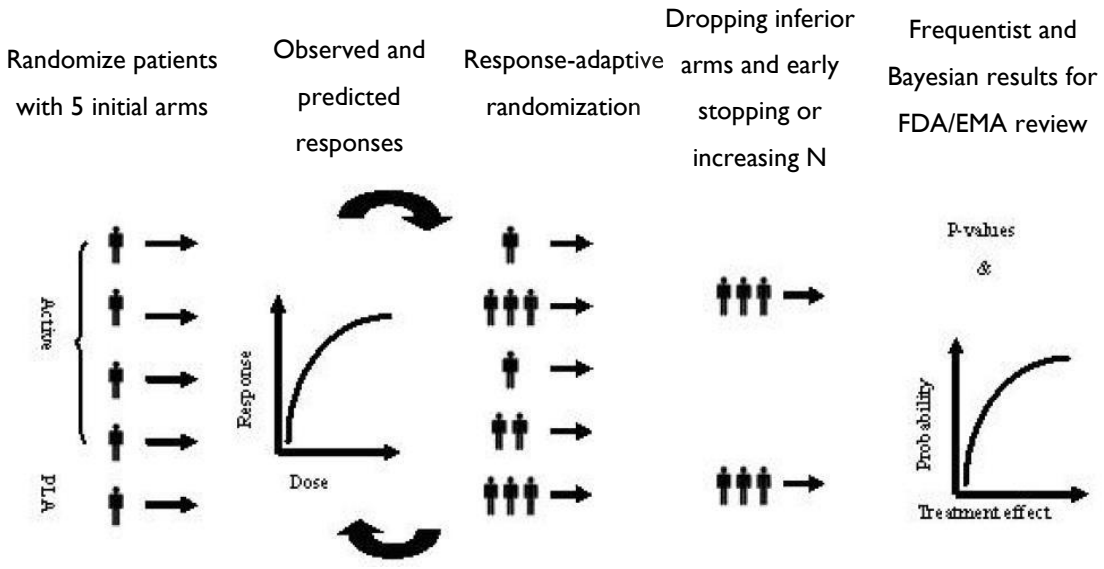


Figure 16 - Schematic Representation of Phase II/III seamless trial design(Chow and Chang, 2008).

Multiple adaptive Design

Finally, this type of adaptive design is a combination of the above designs. Commonly considered multiple-adaptive designs include (Chow and Chang, 2008; Mahajan and Gupta, 2010):

- The combination of adaptive group sequential design, drop-the-losers design and adaptive seamless trial design;
- Adaptive dose-escalation design with adaptive randomization.

Chapter 6: Ethical Issues in Funding Orphan Drug Research and Development

This chapter outlines the moral dilemma of funding orphan drug research and development. Ethical aspects of priority setting for research funding have not been an issue of discussion in the bioethics debate. Conflicting moral obligations of beneficence and distributive justice appear to demand very different levels of funding for orphan drug research. The two types of orphan disease, rare diseases and neglected tropical diseases, present very different ethical challenges to questions about allocation of research funds (Gericke, Riesberg and Busse, 2005). The dilemma could be analyzed considering utilitarian and rights based theories of justice and moral obligations of non-abandonment and a professional obligation to advance medical science.

The decision of how much a society should spend on research on orphan diseases represents a moral dilemma (Gericke, Riesberg and Busse, 2005):

- Each orphan disease only represents a small number of individuals. Investing substantial amounts of resources for rare conditions could be considered unethical from a utilitarian point of view, as it is not maximizing society's benefits, and its opportunity cost in terms of benefits foregone for others are important;
- Many would upload that society has a moral obligation not to abandon individuals who have had the bad luck to be affected by a rare condition for which no treatment exists.

This moral dilemma should be analyzed according to the principle approach of biomedical ethics developed by Beauchamp and Childress (Gericke, Riesberg and Busse, 2005; Paola, Walker and Nixon, 2010):

Justice

Philosophical accounts interpret justice as fair, equitable and appropriate treatment in the light of what is due or owed to individuals (Gericke, Riesberg and Busse, 2005).

Maximizing principles require that health care be distributed so as to achieve maximum benefit. Need principles require distribution of resources in proportion to need. Egalitarian principles

require resources to be distributed so as to reduce inequality (Gericke, Riesberg and Busse, 2005)

Another problem is the extreme uncertainty of benefits: uncertainty of costs and benefits can be take into account in a sensitivity analysis (only 1 in 10 pharmaceutical compounds is successfully marketed) (Wizemann, Robinson and Giffin, 2009; Field and Boat, 2010).

Tropical diseases are diseases with high prevalence in developing countries and do not represent profitable market (only 10% of global health research funding is allocated to 90% of world's health problems) (Hunt and Khosla, 2008).

But does a moral obligation to distribute resources fairly extend to individuals outside the economic, legal and political remit of the society providing the research funds? Applying traditional economic evaluation to such problems is likely to fail, as maximizing global health with national funds of single countries would not be politically acceptable in any country (Gericke, Riesberg and Busse, 2005).

In most industrialized democracies institutions exist that assure everyone access to needed services regardless of ability to pay. In some countries, such Portugal and The Netherlands, the right to health care is protected constitutionally. The French and German constitutions contain a legal obligation to assist individuals in danger, which could potentially apply to the development of treatments for life threatening orphan diseases. The EU Charter of Fundamental Rights (section 35, 2000/C 364/01), states that "everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices".

Beneficence

Beauchamp and Childress understand beneficence broadly, including "all forms of action intended to benefit other persons" or "to contribute to their welfare". Beneficence requires that agents take positive steps to help others, not merely refrain from harmful acts, or to treat individuals autonomously. This principle refers to a moral obligation to further their important and legitimate interests (Gericke, Riesberg and Busse, 2005; Paola, Walker and Nixon, 2010).

The utilitarian understanding of the principle of beneficence has been outlined above with regard to funding decisions for orphan drug research. To discussion the notion of positive beneficence in this context, I will consider the moral obligation of non-abandonment and advancing scientific knowledge as a professional and societal moral obligation (Table 15).

Table 15 - Moral obligation of non-abandonment and advancing scientific knowledge in context of orphan drugs (Landman and Henley, 1999; Gericke, Riesberg and Busse, 2005)**.**

Non-abandonment	Advancing Scientific Knowledge
Health is a basic need and highly specialized health care is an intermediate need necessary. Every patient would have an equal chance to get the health care services necessary. Non-abandonment takes seriously one of the basic elements of a just health care system: fair distribution of the burdens of rationing. Laws and regulations passed to provide incentives for orphan drugs to achieve this principle.	WHO proposed 5 steps: -Measurement of burden of diseases -Risk factor analysis -Assessment of the knowledge base -Cost-effectiveness analysis -Calculation of the present level of investment into research for the condition Venture capitalists discovered that the study of rare diseases often repays research efforts manifold with medical insights and useful drugs for common diseases.

Chapter 7: Neglected Tropical Diseases: Challenges, Progress and Opportunities

WHO defines neglected tropical diseases (NTDs) as "chronically endemic and epidemic-prone tropical diseases, which have a very significant negative impact on the lives of poor populations and remain critically neglected in the global public health agenda" (Liese, Rosenberg and Schratz, 2010).

NTDs are a set of 20 diseases affecting nearly 1 billion people in the world's most impoverished regions: 17 neglected topical diseases, in addition to the so-called "big 3": malaria, tuberculosis and HIV/SIDA (Cohen, Sturgeon and Cohen, 2014). It is estimated that these diseases cause 35,000 deaths per day worldwide.

Thus far yet until recently, the pharmaceutical industry and global policy-makers paid little attention (Hotez, 2013; Cohen, Sturgeon and Cohen, 2014). Of a total of 1395 new drugs approved between 1975 and 1999 in the EU, only 13 drugs (1%) were specifically indicated for a tropical disease (Trouiller *et al.*, 2002; Gericke, Riesberg and Busse, 2005).

Although, existing treatments for killer infectious diseases are increasingly ineffective due to poor diagnostic options, growing drug resistance, unaffordability, poor distribution and inadequate health systems. Lack of scientific knowledge is not the major barrier to drug development – more is known about the biology, immunology, and genetics of leishmanial and trypanosomes than any other parasites. Nor does the gap lie with technology, which has greatly benefit from recent advances. Policy issues seem to be the main obstacle to the translation of this knowledge into actual benefit for patients (Baquero, Coque and Cantón, 2002).

Beginning in the late 1990s, the Bill and Melinda Gates Foundation has committed significant resources earmarked for NTDs drug development. Since then, an array of high-profile product development partnerships (PDPs) has been established, such as the Medicines for Malaria Venture(MMV), Drugs for Neglected Diseases Initiative(DDNi), and TB Alliance (Cohen, Sturgeon and Cohen, 2014).

PDPs are nonprofit public-private partnerships (PPPs) created to advance research and development through collaboration among public sector entities, such as the WHO,

philanthropic sources and the public sector. Partnerships also often involve nonmonetary donations from pharmaceutical firms, or they entail a firm holding the intellectual property for the product being developed. The mission is to develop drugs that address the health needs of vulnerable populations in the developing world (Trouiller *et al.*, 2002; Cohen, Sturgeon and Cohen, 2014).

Increased funding in research and development that is focused on neglected disease drug development seems to be producing results. Approvals targeting neglected diseases and products in phase III trials have shown a steady increase since 2000, with nearly a doubling of products in the period 2009-2013 compared with 2000-2008 in terms of the annual average yield (Cohen, Sturgeon and Cohen, 2014).

One of the first internationally coordinated initiatives addressing a NTD was the Onchocerciasis Control Programme (OCP), which was conceived as early as in 1968, and launched in1974, with co-sponsorship by WHO, the World Bank, UNDP, and the Food and Agriculture Organization (Liese, Rosenberg and Schratz, 2010).

But in the late 1970s and 1980s, resources and the political momentum for control of tropical diseases dwindled, partly because of the failure of the malaria eradication programme and a shift of focus to the social and equitable dimensions of health in the form of primary health care. By the late 1980s, another public health issue gained prominence, which increasingly dominated and continues to dominate the discourse in popular culture, academia, and even the security and intelligence community – the HIV/AIDS pandemic. An exclusive innovative financing mechanism was set up for HIV/AIDS, malaria, and tuberculosis in the form of the Global Fund, while funding for neglected tropical diseases remained limited to a few donors (Liese, Rosenberg and Schratz, 2010).

Later in 2003 and 2005, two workshops in Berlin, co-hosted by the German Agency for Technical Cooperation and WHO, refocused attention towards so-called neglected diseases. In the first workshop, participants called for an integrated approach towards these diseases both for efficacy and advocacy reasons. The second workshop concluded that the burden of disease shared by all the NTDs justified an increased share of resources, that low-cost and cost-effective interventions were widely available, and that some integration or co-implementation was possible (Liese, Rosenberg and Schratz, 2010).

Over the years, health-care systems in developing countries have attempted to improve health status with public health interventions (eg, vaccinations, health education, vector control, and drug treatment programs) for diseases that cause the greatest burden of ill health. Basic health service focused on clinical care through the development of a network of clinics to treat the most common conditions (Gyapong *et al.*, 2010).

Since 2000, many countries have made attempts to restructure and improve their health delivery system through strategic documents, implementation of the sector-wide approach, and strengthening district health systems. However, most health systems in disease-endemic countries continue to face many challenges (Gyapong *et al.*, 2010; Liese, Rosenberg and Schratz, 2010).

The Bill & Melinda Gates Foundation announced a new catalytic investment to build regional funding to support integrated control and elimination strategies for neglected tropical diseases worldwide, and to leverage additional investments in support of a global campaign, called "End the Neglected 2020" in partnership with WHO (Molyneux, 2010).

Drugs for Neglected Disease initiative is screening more than 7000 compounds (The Lancet, 2014). More than 70 countries have now developed national NTD plans. Brazil, with the largest NTD burden in the Americas, included NTD programs in its Without Extreme Poverty plan and launched as school-based strategy combining deworming and leprosy screening (Hotez and Fujiwara, 2014). Colombia became the first country in the world to eliminate onchocerciasis (WHO, 2013).

Despite impressive progress, the fight is far from over. Only 36% of people in need of NTD drugs worldwide received what they needed. Several indicators are not yet on target to achieve the 2020 goal to control NTDs (The Lancet, 2014).

Chapter 8: Pharmacoeconomic Analysis of Orphan Drugs

Pharmacoeconomics has been defined as the description and analysis of the cost of drug therapy and healthcare system and society. More specifically, pharmacoeconomic research is the process of identifying, measuring and comparing the costs, risks, and benefits of programs, services, or therapies and determining which alternative produces the best health outcome for the resource invested (Dipiro, 2012). The products and services delivered by today's healthcare professionals should demonstrate pharmacoeconomic value – that is, a balance of economic, humanistic, and clinical outcomes (Figure 17).

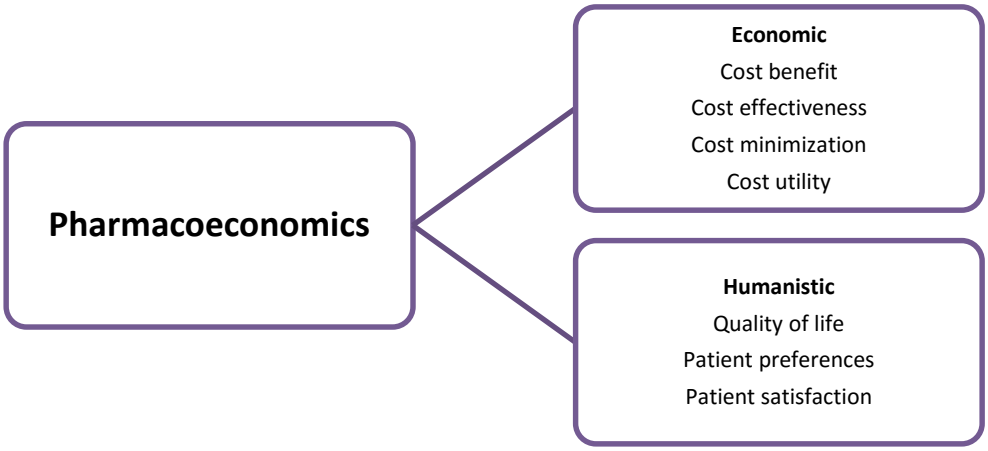


Figure 17 - The pharmacoeconomic methods of evaluation. Adapted from (Dipiro, 2012).

One of the primary applications of pharmacoeconomics in clinical practice today is to aid clinical and policy decision making. Through the appropriate application of pharmacoeconomics, practioners and administrators can make better, more informed decisions regarding the products and services they provide. Complete pharmacotherapy decisions should contain assessments of three basic outcomes areas whenever appropriate; economic, clinical and humanistic (ECHO) (Dipiro, 2012).

8.1 Market Approval and Market Access

Orphan drug development is a three-step procedure and the two first steps have been already discussed in earlier chapters: orphan designation, and marketing authorization, which both occur at the regulatory centralized level. The final step occurs at the payer's level, which in

Europe is at the national level and in the USA is at the level of the Health Maintenance Organizations (HMOs). HMOs are organizations that provide or arrange managed care in liaison with healthcare providers, like hospitals, doctors, on a pre-paid basis, through insurance contributions (Hernberg-Sthal and Reljanovic, 2013).

For a drug to obtain marketing authorization, regulatory agencies (FDA/EMA) examine the properties of the drug to determine whether it has been shown to be safe and effective in the defined patient population. Therefore, after MA has been granted, orphan (and non-orphan, also) drugs must go through further pricing and reimbursement processes at the national level.

Thus, payers need to consider whether it is worthwhile paying for the drug, given the complexities of reimbursement, together with the limited budgets often available. Several health-economic models have been developed to help decide whether the additional clinical benefit of the new drug, when compared to available treatment, is: 1) worth paying for and 2) affordable (Hernberg-Sthal and Reljanovic, 2013).

Payers have taken different approaches to finding answers to these questions including the use of health technology assessment (HTA) methodologies (Stephens, Hanke and Doshi, 2012).

Given that there is a centralized process for the MA of drugs and a decentralized process for pricing and reimbursement decisions, it is not surprising that there are differences in patient access to new treatments between MS in Europe. This applies for both orphan and non-orphan drugs, but the combination of higher price and smaller datasets for orphan drugs can tend to amplify the challenges for orphan drugs (Hernberg-Sthal and Reljanovic, 2013).

In the USA there are differences between the various insurance plans offered by the HMOs and between different drugs depending on insurance coverage. In most countries in Europe, the national HTA processes are not adapted accordingly, which leads to orphan drugs not fulfilling payers' criteria for reimbursement of the drug. This has led to various initiatives from both government and patient advocacy groups to develop new health economic models for orphan drugs (Hernberg-Sthal and Reljanovic, 2013).

In general, the price of a drug and the corresponding cost-per-patient are determined by the size of the patient population requiring therapy and by the risk taken to develop the product, which is reflected in the potential return on investment (Figure 18). It can therefore be seen

that higher-risk projects, such as research into rare diseases and orphan drugs, will likely require higher potential return on investment to find enough investors support, which results in a higher cost to the patient.

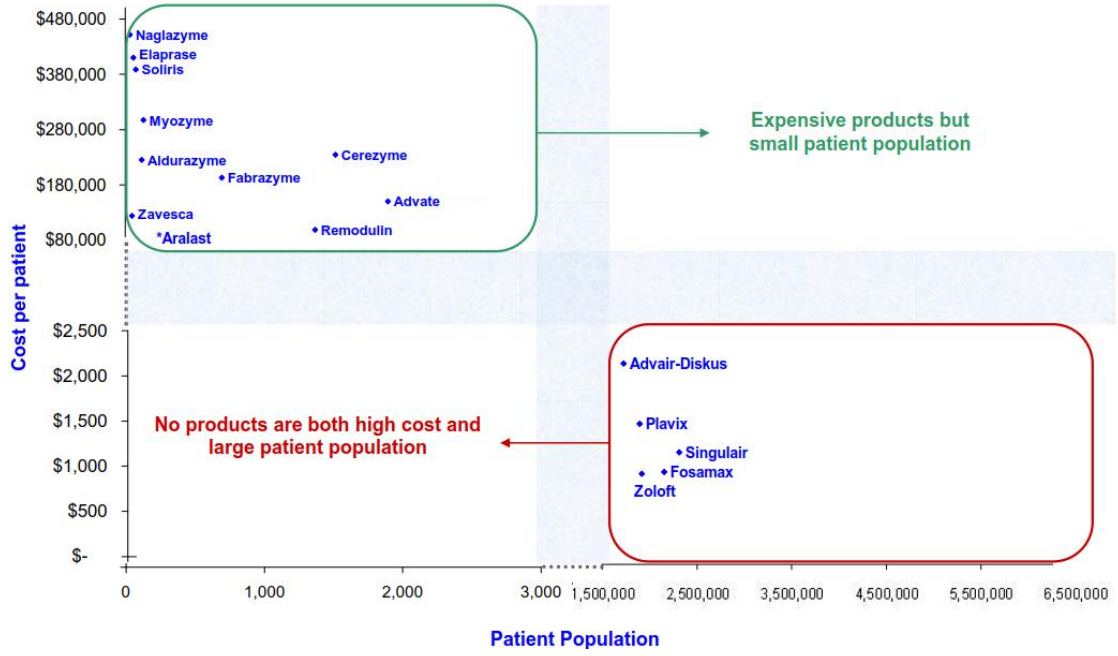


Figure 18 - Price per Patient it is function of Patient Population. Adapted from (Genzyme, 2007).

If payers are not prepared to reimburse treatment this could have a serious negative impact on patient access to much-needed drugs, and incentives provided to the pharmaceutical industry through legislation to promote the development could be seen as a waste of money, which puts into question the concept behind drug legislation (Hernberg-Sthal and Reljanovic, 2013).

Policymakers and healthcare payers are, today, increasingly using HTA, including economic evaluations and budget impact analyses, for reimbursement decisions. National pricing and reimbursement regimes vary significantly among MS, although initiatives to facilitate understanding and shared approaches to evaluations that may be carried out in different countries have been explored in recent years, for example EUnetHTA launched by EC (Hernberg-Sthal and Reljanovic, 2013; Hyry *et al.*, 2014).

A European working group has recommended a preliminary assessment matrix for optional use by EU Member States to harmonize access to orphan therapies, incorporating as one

factor cost-effectiveness (though there is no consensus as to convert the matrix into a numerical formula for funding decision-making) (Hyry *et al.*, 2014).

8.1.1 Public Involvement in Orphan Drug Coverage Reimbursement Decision-Making

Over the past twenty years there has been a considerable increase in the active involvement of publics and patients (Ps&Ps) in healthcare and research (Douglas *et al.*, 2015). By the way, patient involvement since early was crucial in orphan drugs policy development. Reimbursement decision-making for orphan drugs poses supplementary challenges to the ones already facing decision-making for common drugs or other areas of research and care. All allocation decisions have implications for the kind of health care that will be available, and therefore benefit from involvement of Ps&Ps (Douglas *et al.*, 2015).

A recent survey of members of the International Network of Agencies for Health Technology Assessment (INAHTA) found that 22 agencies involved "consumers" in some aspects of their HTA programs, which ranged from seeking comments for refining the scope and nature of HTA projects, or even deeper involvement such as committee participation in the development of HTA protocols (Douglas *et al.*, 2015).

The following table (Table 16) shows the possibilities for Ps&Ps involvement in decision making for orphan drugs, specified by Abelson and colleagues.

Table 16 - Framework for involvement in HTA and coverage policy decisions. Adapted from (Douglas *et al.*, 2015)**.**

Goal of involvement	Group of tasks	Form of involvement	Accountability mechanisms	Example in orphan drugs
Instrumental	Technology assessment; Criteria development	Institutionalized involvement	Answerability, citizen engagement	Citizen's Council on Orphan Drugs; Patient Task Force for Criteria Development;

Goal of involvement	Group of tasks	Form of involvement	Accountability mechanisms	Example in orphan drugs
Democratic	Priority setting	Direct involvement	Answerability, citizen engagement, sanction and appeals	Deliberative event that procedures members to sit on decision-making body
Development	Priority setting, criteria development	Ad hoc involvement	Answerability, citizen engagement, sanction and appeals	Town hall meeting or national televised debate

8.2 Orphan Drugs: A new big commercial opportunity

As I have already been discussed throughout this dissertation, a small market is generally viewed as a disincentive for the development of drugs. Many of the costs of developing a new drug are incurred regardless of the size of the potential market. However, if a company can set a price that is high enough to recover its costs and generate profits because enough public and private health insurance plans and patients and families will pay that price, then a manufacturer may not be deterred by a small target market (Field and Boat, 2010).

In fact, orphan drugs can be very profitable. In addition to incentives for developing orphan drugs provided by the legislation, the potential profitability of orphan versus non-orphan drugs may be affected by other factors: private health plans generally have little leverage in negotiating prices for expensive biotechnology drugs, many of which are orphan drugs (Field and Boat, 2010; Wellman-Labadie and Zhou, 2010):

- The lack of competitors in the market for a drug, which gives a manufacturers little reason to offer discounts;
- Limited volume of a drug used by the plan, which limits a plan's negotiating power.

Currently, orphan drugs are an attractive commercial opportunity: according O. Wellman-Labadie and Y. Zhou, a total of 43 brand name drugs with global annual sales of greater than

a billion US $, were identified to have orphan designations. Of these, blockbusters, 18 were approved solely as orphan drugs in the US. Within these 18 orphan blockbusters drugs, 11 have reached blockbuster status within the 7 years orphan drug market exclusivity period (Wellman-Labadie and Zhou, 2010).

Once a product has obtained orphan drug exclusivity, the FDA cannot approve a new brand name or generic drug application for the same product and for the same rare disease indication. On the other hand, the same drug can obtain approval for a different disease indication and there is no limit on the number of drugs that may be designated for a specific disease.

In addition, pharmaceutically active agents such as interferon, somatropin and levocarnitin, among others, can obtain up to 33 orphan designations each. Orphan drugs, intended to treat small patient populations, become drugs which treat large populations through the addition of orphan drug niches and thereby violate the "less than 200 000 patient population" clause. Hence, initially unprofitable orphan drugs potentially reach blockbusters status due the multiplication and extension of indications (Wellman-Labadie and Zhou, 2010). In order to address the issue of profitable drugs which have been benefited from orphan drug incentives, initiatives from Japan could be considered: in Japan, pharmaceutical manufacturers are mandated to pay a one-percent sales tax on orphan drugs with annual profits exceeding 100 million yen until government subsidies received by manufacturers have been repaid. Considering that both Japan and the EU offer 10 years market exclusivity, the Japanese Orphan Drug Act appears to me more successful in stimulating orphan drug R&D, as deduced by drug approvals (Wellman-Labadie and Zhou, 2010).

No doubt that Orphan Drug legislation dramatically changed rare diseases research as well as the development of pharmaceutical agents. Before ODA, pharmaceutical industry focused on large disease populations in order to maximize returns, as previously discussed. However, orphan drugs are now seen as big "moneymakers". Despite their relatively limited populations, orphan drugs have already demonstrated significant financial value. For instance, Rituxan (rituximab) – an orphan treatment marketed by Genentech, a wholly owned subsidiary of Roche and Biogen Idec, for non-Hodgkin's B cell lymphoma and for chronic lymphocytic leukemia – is now the world's second most profitable drug after Pfizer's blockbuster Lipitor (atorvastatina calcium). Moreover, a report by EvaluatePharma projects the Rituxan will

become the world's best-selling orphan drug in 2018, generating more than $6,9 billion in sales (Ted, 2014).

In fact, the report from EvaluatePharma demonstrate that the average return on investment for orphan drugs is nearly double that for non-orphan drugs: $14.90 vs. $7.90 for every dollar invested in Phase III trials, respectively. This is due partly to lower Phase III trial costs for orphan versus non-orphan drugs (with most products costing $97 million vs. $143 million or more to develop, respectively), which, in turn, are due mainly to smaller trials (with most products requiring 538 vs. 1,491 subjects or more, respectively) (Public Citizen, 2015).

The economics and investment case for orphan drug development and commercialization are more favorable compared with non-orphan drugs. This is remarkable given the smaller target patient populations for orphan diseases. There are a number of key drivers that could explain the favorable economics for orphan drugs: R&D related drivers or commercial-related drivers, presented on Figure 19 (Meekings, Williams and Arrowsmith, 2012).

As discussed in chapter 5, clinical trials on orphan drugs can be shorter compared with non-orphan drugs (3,9 years vs 5,4 years) and regulatory filings are more successful for orphan drugs (93% of probability of success vs 88%) (Meekings, Williams and Arrowsmith, 2012).

In summary, taken together, lower costs, higher rates of regulatory success and parity of revenue-generating potential translate into higher profitability of orphan drugs versus non-orphan drugs.

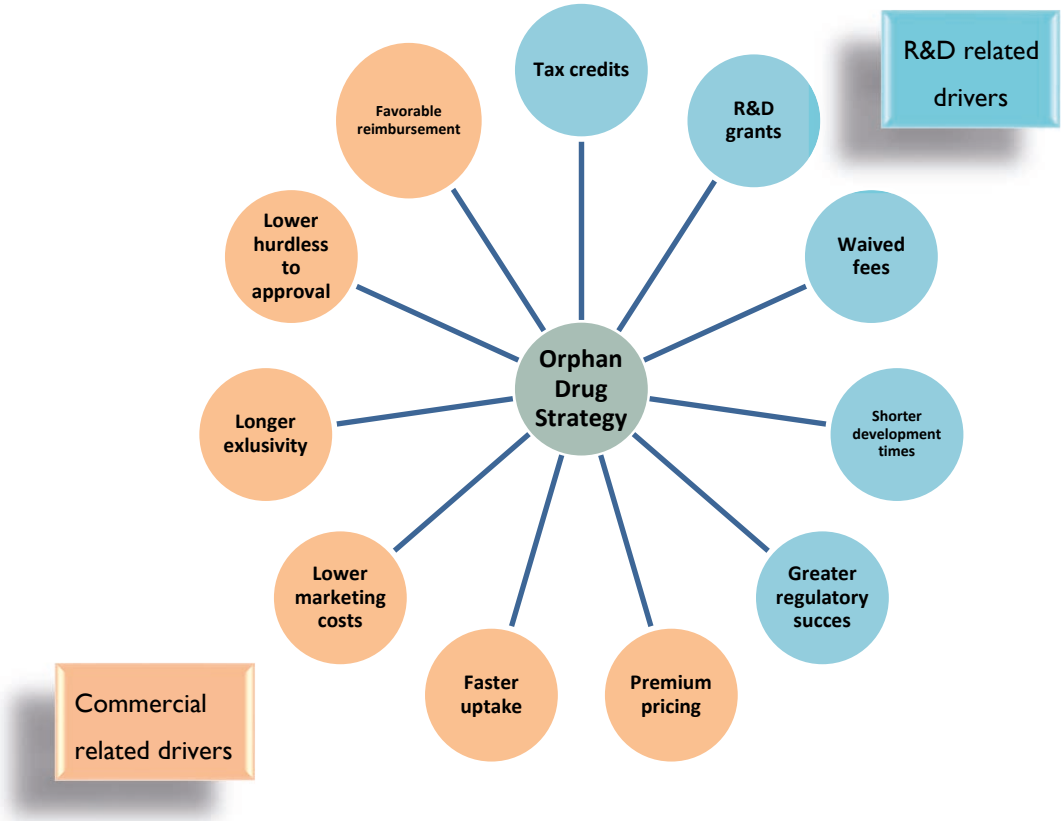


Figure 19 – Summary of incentives for orphan drug development. Adapted from (Meekings, Williams and Arrowsmith, 2012)**.**

8.3 Orphan Medicines Consumption in Portugal

In Portugal, the use of orphan drugs is carried out mainly in hospitals, which is why it was considered important to present an analysis of the evolution of consumption of these medicines in National Health Services between 2007-2014 (INFARMED, 2016).

It is observed that the expense of National Health Services hospitals with orphan drugs has shown an increase over the past few years, with only decreased from 2011 to 2012 due the loss of orphan designation by Imatinib, in April 2012 (Figure 20). Between 2007 and 2014 the increase in spending on orphan drugs was 94 percent, reaching in 2014 the value of 74,9 M euros, representing about 7,8% of hospitals charges for drugs in that year (INFARMED, 2016).

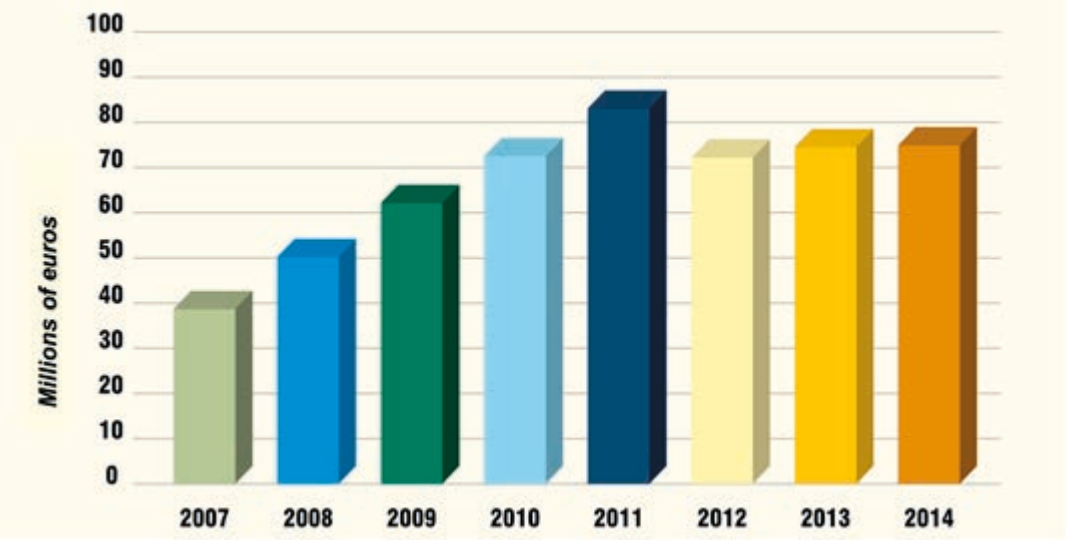


Figure 20 - Expenditure on orphan medicines in Portugal hospitals between 2007 and 2014.Adapted from(INFARMED, 2016).

The analysis of orphan drugs by therapeutic indication reflects the therapeutic area (Figure 21) with the greatest weigh in 2014 charges was cancer, with a 38% weight, followed by amyloid polyneuropathy with 24% and lysosomal disease 20%. The expense related to pulmonary hypertension was 7% and decreased relative to 2013 due the loss of orphan designation for Bosentan in April 2014. The "other" conditions include 27 drugs, corresponding on 11% of the burden of orphan drugs (INFARMED, 2016).

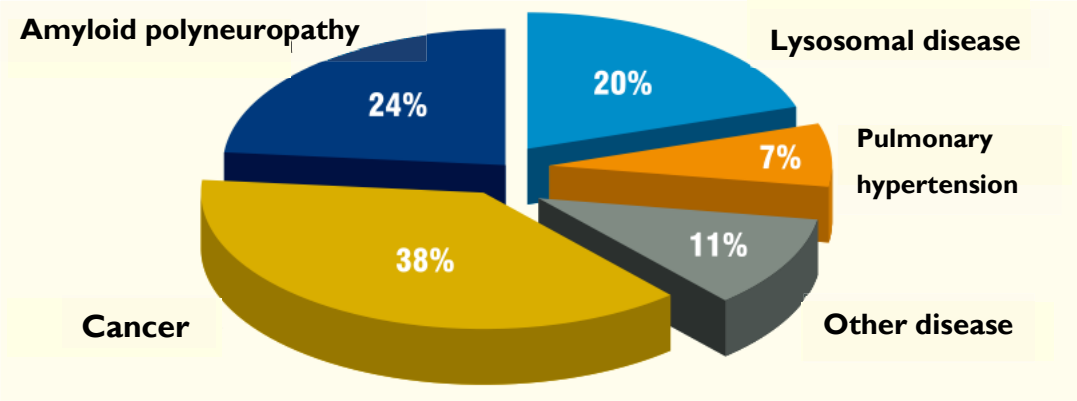


Figure 21 - Distribution of hospital charges for orphan medicinal products for pathology in 2014. Adapted from (INFARMED, 2016).

Analyzing Figure 22, the therapeutic area with more weight in expenditure was cancer. Imatinib was the medicine with more weight in expenditure on orphan medicines in 2011, representing the consumption of this medicine about 2% from the total consumption of medicines in

hospitals. The second area with higher charges corresponding to the lysosomal diseases (INFARMED, 2016).

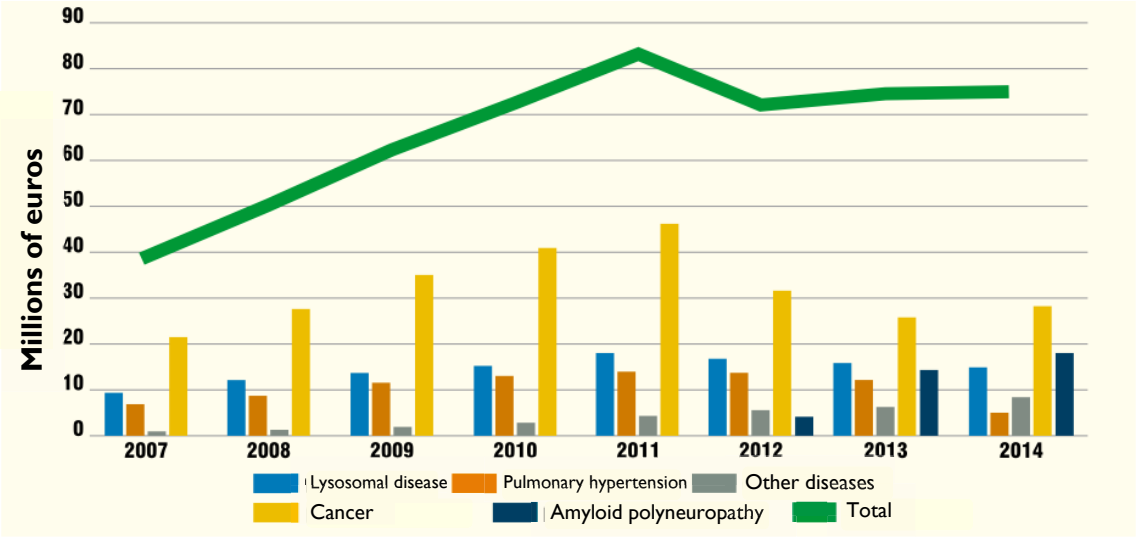


Figure 22 - Hospital expenditures with Orphan Medicines, by disease, between 2007 and 2014. Adapted from(INFARMED, 2016).

According INFARMED, in 2015 there was an increase by 14,2% in expenditures on orphan drugs over the same period 2014 (INFARMED, 2015). An official report from INFARMED shows that the global expenditure with orphan medicines in 2015 increased more than 10% and reached 82,2 M euros (8% of total expenditures with drugs).

This brief analysis is concluded that there is an increase in expenditure orphan drugs in Portugal due drug approval with the increase market authorization of medicines with orphan designation and increase accessibility in Health National Service hospitals (INFARMED, 2016).

Chapter 9: Future Perspectives

As has been discussed previously in this dissertation, facts and figures about rare diseases are increasingly visible and the number of medicines available is substantially higher nowadays. Although there is no internationally accepted definition of rare diseases: in the USA, rare diseases are those that affect fewer than 200 000 (7.5 in 10 000); In the EU, a rare disease affect fewer than 5 In 10000; In Japan, the prevalence of a rare disease is fewer than 4 in 10,000 (Tobergte and Curtis, 2011; Song *et al.*, 2012; Richter *et al.*, 2015). Taking into account that these three geographical areas are part of the International Council for Harmonization (ICH), is expected that a common definition and maybe common incentives from these three parts, emerge in the future.

As mentioned in 1.1, some rare conditions are extremely rare, with the number of reported cases in the single or low double digits (Field and Boat, 2010). Others occur in hundreds, thousands or tens thousands of people. Obviously small rare disease groups are less visible compared with the bigger rare disease foundations (Beck, 2012). Thus, another important issue also related to the lack of universal definitions, is the case of ultra-rare disease: there is no formal definition but the National Institute of Clinical Excellence (NICE) uses the term for diseases affecting fewer than 1000 people in England and Wales; in the USA, an ultra-rare orphan disease is defined as a disorder that affects 2000 people (Dear, Lilitkarntakul and Webb, 2006; Beck, 2012). Therefore, it is expected that in the future an internationally accepted definition for ultra-rare diseases could be created and the orphan legislation should change according to specific needs of these patients. Additional incentives should be considered, eventually. In fact, only 11% (144/1310) of orphan designations were for ultra-rare diseases (Wood *et al.*, 2013). Also more collaboration and coordination between rare and ultra-rare disease foundations working in similar areas might be needed, like Sanfilippo Foundations, for example. Bringing closely related diseases together will increase the patient population and attractiveness to facilitate venture funding and commercial interest.

Conclusion

The spiraling cost of drug development in tune with stringent regulations, coupled with the low return on investment, often tends to discourage pharmaceutical innovators from developing products for extremely small patient populations. Rare diseases in small patient populations thus 'orphaned' by the pharmaceutical industry, having but a few approved drug treatment options available are called 'orphan diseases' (Sharma *et al.*, 2010).

Pharmaceutical products for diseases can become neglected for two major reasons: when there are too few patients to offer a market large enough to justify the cost and risk of the research and development required to bring a drug to market (rare diseases) and when there are larger numbers of very poor patients (neglected tropical diseases).

As discussed before, in this dissertation, several industrialized countries have passed specific legislation defining epidemiological or/and economic criteria for designation of orphan status and incentives to counteract the neglect of orphan diseases in industrial research. After the launch of the US Orphan Drug Act in 1983, Japan (1993), Taiwan and Australia (1997), and lately the European Union, in 2000, have passed laws to incite the pharmaceutical and biotechnological industries to pursue research on orphan drugs by providing tax breaks and market exclusivity (Gericke, Riesberg and Busse, 2005).

The prevalence threshold defining a rare disease, in order for it to benefit from advantages of orphan status, is established, in relative terms, at fewer than 5 persons per 10,000 inhabitants (Europe) or, in absolute terms, at fewer than 200,000 persons (United States of America). To these epidemiological criteria are added economic considerations. A drug receives orphan designation if it is used to treat a disease whose prevalence is so low that, in absence of incentives, commercializing the drug would unlikely generate sufficient revenues to absorb the costs related to its development and marketing (Côté and Keating, 2012).

The decision to pass the ODA was based on the belief that pharmaceutical companies would otherwise fail to develop orphan drugs because these treatments generate relatively small sales and consequently fail to turn high profits after accounting for resources spent on research. Yet now, more than three decades after the passage of the ODA, the landscape of orphan drug development has changed dramatically. Currently, drug development for the rare

disorders is far exceeding anything seen in the common diseases (Castellani, 2011; Public Citizen, 2015).

In the United States (USA), between 1983 and 2014, more than 350 drugs have been approved to treat rare diseases, compared to fewer than 10 in the 1970s (Castellani, 2011; Wilding *et al.*, 2013). Moreover, the Orphan Drug Act of 1983 provided incentives, for example a longer period of marketing exclusivity, for drugs that are not expected to recoup their development costs or that are targeted at diseases affecting fewer than 200,000 people. By 2011, the US Food and Drug Administration had designated over 2300 medicines as orphan drugs. Meanwhile, in Europe, 20% of the innovative products with marketing authorization (MA) were developed for rare diseases (Berman, 2014). In the European Union, between 2000 and 2010, more than 850 orphan drug designations have been granted by the European Commission and more than 60 orphan drugs have received marketing authorization (COMP, 2011).

Over the last years, new medicines have been approved for many genetic disease, rare cancers and myelodysplastic syndromes (NIH, 2013). This ongoing innovation and the hundreds of new medicines in development offer hope that physicians will have new treatment options for patients confronting a rare disease (NIH, 2013).

It is interesting to note that patient engagement and empowerment through the establishment of patient networks and advocacy groups is of special importance in the rare diseases field. As discussed previously in this dissertation, patient organizations are currently active in many ways: they increase public awareness, collect information about rare diseases, provide support and information to affected families, encourage basic research and grant funds, maintain patient registries and collection of specimens in biobanks, and network with universities, industry, and health authorities (Hernberg-Sthal and Reljanovic, 2013).

Though registration requirements for orphan drugs are not fundamentally different from other medicinal products, obvious obstacles are given by the disseminated and limited number of patients with a specific rare disease, limited knowledge of disease natural history, validation of clinical endpoints and ethical problems by using placebo. Thus, adaptive clinical trials may be used and there are a lot of possibilities which can give flexibility and efficiency that are needed in the development process (Chow and Chang, 2008; FDA, 2010; Hernberg-Sthal and Reljanovic, 2013).

Market access for orphan drugs also have many challenges for patients, payers and legislators: disparate data requirements behind EU centralized regulatory approval and local drug reimbursement, coupled with scarcity of patients and lack of information surrounding rare diseases. Currently there is no centralized or uniform mechanism considering these facts, which has led to inconsistency in patient access to orphan drugs between European countries. Initiatives such as the Clinical Added Value of Orphan Medicinal Products (CAVOMP) aim to identify approaches to streamline the processes, coordinate activities, make better use of available data, and ensure earlier interactions with payers within the drug development process, in order to help meet their requirements (Wizemann, Robinson and Giffin, 2009; Hernberg-Sthal and Reljanovic, 2013).

Despite the progress in the field of rare diseases, there is still a need of investment in neglected tropical diseases which pipeline is very limited. To deliver new therapies for NTDs it is necessary (Wizemann, Robinson and Giffin, 2009): explore new business model and new source of capital; establish public-private partnerships (such as the Medicines for Malaria Venture, Drugs for Neglected Diseases Initiative, Global Alliance and Institute for One World Health); create new incentives to train and retain health care professional in developing countries in performing clinical trials at a level that is acceptable for regulatory approval; ensure political will and a global community to deal with corruption in developing world and enforce intellectual property rights and advocate for policies that sustain and stimulate innovation (Guy, 2007; Hotez, 2013; Utzinger and Keiser, 2013).

One of the most interesting point is related to the commercial opportunity of orphan drugs. In fact, several widely recognized specialty drugs have made headlines in recent years, as their annual sales have skyrocketed into the billions, far beyond their original orphan market potential, thanks to added label indications (as well as off-label use). According to Dorholt of Accredo, nearly 18 orphan drugs have received blockbuster sales on expanded US indications alone, and at least nine orphan drugs have received blockbuster status within one year of FDA approval as orphan drug (Shelley, 2015).

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