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# Les législations des médicaments orphelins : de la conception à la dispensation

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**THESE**

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**EN VUE D'OBTENIR**

**LE DIPLOME D'ETAT DE DOCTEUR EN PHARMACIE**

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DE LA CONCEPTION A LA DISPENSATION**

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## **RESUME**

Les médicaments orphelins – des traitements des maladies rares, sont devenus une tendance émergente dans l'industrie pharmaceutique depuis quelques décennies. Grâce aux investissements des entreprises pharmaceutiques et aux mesures incitatives des autorités de santé, la recherche et le développement des maladies rares ont obtenu des résultats révolutionnaires. De nombreuses maladies rares peuvent désormais être traitées. L'espérance de vie et la qualité de vie des patients sont considérablement améliorées. Alors que le cadre réglementaire sur les médicaments orphelins a été créé pour la première fois il y a 36 ans et qu'il est en évolution constante, le développement d'un nouveau médicament orphelin rencontre de nombreuses difficultés notamment dans la recherche précoce, les essais cliniques et l'accès aux patients. D'une autre coté, nous avons aussi observés une croissance remarquable des connaissances des séquences génétiques et des biotechnologies. Ceci a permis d'ouvrir la porte à de profondes compréhensions de physiopathologies et d'offrir plus de possibilités de traitements. En raison de l'évolution rapide du marché des médicaments orphelins, il est nécessaire d'avoir une vision exhaustive des exigences réglementaires de la recherche précoce jusqu'à la distribution aux patients afin d'identifier les difficultés et ainsi les opportunités pour les acteurs de santé concernés.

## **ABSTRACT**

Orphan drugs - treatments for rare diseases, have become an emerging trend in pharmaceutical industry since the last several decades. Thank to investments from pharmaceutical companies and incentives from health authorities, research and development in rare diseases has achieved significant ground-breaking outcomes. Many rare diseases now can be treated. Patient's condition and life quality have been significantly improved. As the legislation background for Orphan Drugs was first created 36 years ago and is still evolving these days, developing a new orphan drug encounters numerous difficulties in different phases, especially in early drug discovery, clinical trials, and patient access. On the other side, the knowledge about genetic sequence and biotechnologies have significantly increased, which facilitates the research and development of orphan drugs. Due to a rapid growth in orphan drugs market, it is necessary to have a comprehensive understanding on regulatory requirement worldwide from early research to patient distribution, in order to identify challenges and also opportunities for concerned healthcare players.

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## ACRONYMS

AFIFA	Agenzia Italiana Del Farmaco Italian Medicines Agency
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz German Pharmaceuticals Market Reorganisation Act
ANSM	Agence Nationale De Sécurité Du Médicament Et Des Produits De Santé French Medicines And Health Product Agency
ASMR	Amélioration Du Service Medical Rendu Added Therapeutic Value
ATMP	Advanced Therapeutic Medicinal Product
ATU	Temporary Use Authorisation
BLA	Biologics License Application
BPCA	Best Pharmaceuticals For Children Act
BFAM	Bundesinstitut Für Arzneimittel Und Medizinprodukte German Medicines Agency
CAT	Committee For Advanced Therapies
CBER	Centre For Biologics Evaluation And Research
CDER	Center For Drug Evaluation And Research
CEEPS	Commission Évaluation Économique Et De Sante Publique Economic Evaluation Commission For Public Health
CEPS	Comité Économique Des Produits De Sante Economic Committee For Health Products
CFR	Code Federal Regulation
CFTR	Cystic Fibrosis Transmembrane Regulator
CHMP	Committee For Medicinal Products For Human Use
CJD	Creutzfeldt Jakob Disease
CMS	Centers For Medicare And Medicaid Services Com
COMP	Committee For Orphan Medicinal Products
CPR	Comitato Prezzi E Rimborso Italian Pricing and Reimbursement Commission
CT	Commission De Transparence French Transparence Commission
CUP	Compassionate Use Program
DMD	Duchenne Muscular Dystrophy
DNA	Deoxyribonucleic Acid
EAP	Expanded Access Program
EC	European Commission
EMA	European Medicines Agency

ERT	Enzyme Replacement Therapy
EU	European Union
EUCERD	European Union Committee Of Experts On Rare Disease
EURODIS	European Organization For Rare Diseases
FDA	Food And Drug Administration
G-BA	Gemeinsamer Bundesausschuss German Joint Committee
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GKV-SV	Verbände Der Gesetzlichen Krankenversicherung- Spitzenverband German Central Federal Association Of Statutory Health Insurance Funds
GMA	Arzneimittelgesetz German Medicine Acts
HAS	Haut Autorité De Santé
HBB	Hemoglobin Beta
HTAS	Health Technology Association
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
IMM	Irreversible Morbidity Or Mortality
IND	Investigational New Drug
IQWiG	German Institute For Quality And Efficiency In Health Care
LED	Evaluation And Licensing Division
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MCDA	Multi Criteria Decision Analysis
MHLW	Minister Of Health, Labour And Welfare
NBS	New Born Screening
NDA	New Drug Application
NHI	National Health Insurance
NORD	National Organization For Rare Disorders
OECD	Organization For Economic Cooperation And Development
OOPD	Office Of Orphan Products Development Of Orphan Products Development
PAFSC	Pharmaceutical Affairs And Food Sanitation Council
PAL	Pharmaceutical Affairs Law
PDCO	Pediatric Committee Of European Medicines Agency
PIP	Pediatric Investigation Plan
PMDA	Pharmaceutical And Medical Devices Agency
PREA	Pediatric Research Equity Act
RD	Research And Development

RNA	Ribonucleic Acid
RTU	Recommendation Temporary Use
SHIS	Statutory Health Insurance
SMR	Service Médical Rendu – Therapeutic Value
SSDI	Social Security Disability Insurance
SSN	Servizio Sanitario Nazionale Italy National Health System
UK	United Kingdom
UNCAM	Union Nationale Des Caisses Assurance Maladie French National Union Of Health Insurance Funds
USA	United States Of America
UV	Ultra Violet
WHO	World Health Organization

## **PART I. INTRODUCTION**

According to dictionary, Orphan is defined as a child whose parents are dead. “Orphan” was first used in medical context in an editorial comment “Therapeutic Orphans” by Harry Shirkey in 1968[1]. In his article, he used the term “therapeutic or pharmaceutical orphans” to describe the lack of clinical proof for the efficiency and safety in drugs addressed to children[2]. Since then, the term “orphan” has been using for the rare disease whose therapeutic treatments are abandoned.

The definition of \* being rare \* may be different among countries, however, there is one common characteristic: these pathologies are so rare that the physicians observe less than one case per year. These diseases have incidence at birth less than 1 in 2000; the symptoms may first appear only in late childhood or in adulthood. A rare disease may have different causes and the symptoms may vary from one patient to another, which causes great difficulties in diagnosis and treatment. Because of the lack of knowledge about pathology, diagnosis and a limited amount of patients, the development of therapeutic treatment for rare diseases was not a target in pharmaceutical industry for very long time. Many pharmaceutical companies hesitated to invest on this area because of insufficient return from economic aspect.

However, in the last few years, pharmaceutical industry has experienced a significant evolution such as exhaustion in new chemical therapeutic entities, rise of biotechnology-derived products, more stringent regulatory guidelines, patent expiries and generic trends. Because of all the aforementioned factors, together with the incentives from Health Authorities in both financial and regulatory aspects, rare diseases have become a niche buster in medical research and attracted the investment from big pharmaceutical companies. Since then, general knowledge about rare diseases have also increased considerably.

This thesis is produced to give an overall vision about drug development for rare diseases from research to distribution. The first part of this thesis is to give some general understanding about rare diseases from a global perspective. The second part is dedicated for the regulatory framework for development of orphan drugs in Europe, United State and Japan. The next part of the thesis points out the challenges from both scientific and economic points of view in different

regions. The final part is about the strategies to overcome the difficulties, the opportunities as well as the future of orphan drugs' market.

## PART II. RARE DISEASES FROM A GLOBAL PERSPECTIVE

### A. Definition of Rare Diseases

According to World Health Organization (WHO), a disease is defined as rare if it touches less than 1 in 1000 citizens. However, the definition of \* **rare** \* varies from one country to another. Currently, there is no universal definition for rare diseases[3].

In Europe, according to European Organization for Rare Diseases (EURORDIS), a rare disorder is identified if it affects less than 1 in 2000 people in Europe[4]. This definition was first mentioned in **Regulation 141/2000** on Orphan Drugs, published in 1999[5]. A rare disease is characterized by following factors:

- Chronic, progressive, degenerative, life-threatening and disabling
- Impact patients and their family's life quality. Patients often suffer from a total or partial loss of autonomy, high level of pain.
- Mostly genetic-related
- Absence of curative treatment

It is estimated that 6000-8000 rare diseases are identified in Europe and affect more than 30 million people, which corresponds to 6-8% of the population of 27 countries[6]. Among these patients, 75% are children and 30% of children with rare diseases can live only until their 5<sup>th</sup> birthday[4].

In United States, a disease is identified as *rare* if it affects less than 200.000 people in the United States (**Orphan Drug Act**)[7]. However, in United States, there is no condition about the characteristics of a disease to be defined as *rare disease* like in Europe.

In Japan, for very long time, there was no definition as *rare diseases*. Rare diseases in Japan used to be known as *intractable* until 1993, when the Ministry of Health and Welfare revised their laws. Since then, a disease is called *rare and intractable disease* if it has an “unknown etiology” with no effective treatment and presents a major financial and psychological burden

and rare (less than 50.000 total patients in Japan)[8].

## **B. Epidemiology of rare diseases**

Epidemiology studies are conducted in order to provide information about causal factors of a disease (etiology), the number of affected people (prevalence) or the number of new cases (incidence) within a specific time range.

However, epidemiology research of rare diseases is extremely difficult due to the lack of knowledge, diagnostics, identification, reporting - tracking system. As a result, the epidemiology in rare diseases remains in ambiguity.

A bibliographical study has been conducted by the association of Eurordis and Orphanet in order to characterize the rarest diseases in Europe in numbers: identify the prevalence of each rare disease in term of age of onset, life expectancy and mode of inheritance. The first results were published for 359 rare diseases and a report will be issued every 3 months[9].

### **1. Origins of Rare Diseases**

#### **a. Genetic causes**

According to Eurordis, 80% of rare diseases have genetic origins or genetics components[6] . However, rare diseases can be also resulted from bacterial or viral infections, allergies, environmental factors or degenerative/proliferative causes. Many rare diseases have been recognized for years but the causes remain unknown. For example: Buerger's Disease, which causes the occlusion of intermediate and small arteries and veins of extremities, was first reported in 1879. Until today, no exact cause has been identified, we just know that the use of tobacco is associated with the development of this disease[10].

Rare genetic diseases are caused by the defect of one or multiple mutations on one gene or several genes (mono or multi-genetic disorders) or even on chromosomal scale (chromosome disorders). DNA molecules or deoxyribonucleic acids are constituted by four nucleotides: Adenine, Thymine, Guanine and Cytosine. A gene is a segment of DNA or RNA that will be expressed in a functional proteine. The DNA molecules are tightly coiled around histones proteins and constitute chromosomes. A mutation on a gene is a defect on small scale and is

usually caused by errors in nucleotides placement. A gene mutation can be corrected itself but could also lead to a chromosomal mutation. A chromosomal mutation is a defect on large scale, where the numbers or the structure of chromosomes are altered and is difficult to be corrected.

Cystic Fibrosis or mucoviscidosis, one of the most frequent rare genetic disorders, is caused by mutations in one single gene, the Cystic Fibrosis Transmembrane Regulator (CFTR) gene located on band 31.2 of the long arm (q) of chromosome 7 (7q31.2). In people with Cystic Fibrosis, cells cannot release chloride, which results in a cellular salt imbalance and thick, sticky mucus, dehydration and abnormal functioning glandular. CFTR gene is expressed in the lung, gastrointestinal tract, pancreas, sweat gland and genitourinary system[11].

Multiple mutations in a single gene can cause different forms of a disease because these mutations alter a different gene. For example, the mutations in gene coded for Dystrophin protein in muscle fiber membrane can be expressed in nine different forms, among those the most famous form is the mutation of gene coding for Duchenne muscular dystrophine protein (DMD). Defects of the DMD gene can result to Duchenne muscular dystrophy (absence of DMD) or Becker muscular dystrophy (presence of DMD but non-functional)[12].

A rare genetic disorder can be inherited from parents or can appear as a result of sporadic or chance mutations. Allele is a variation of a gene, located on a specific position on chromosome. As chromosome is in pairs, allele is present one in each pair. Two alleles inherited from parents can be the same or different. When an allele is always expressed, it is dominant. An allele that is not expressed is recessive. A rare genetic disorder can be inherited in a dominant or recessive way. A recessive inheritance is when the child has the recessive disease alleles from both parents, the alleles will be expressed as a disorder. In a dominant inheritance, the child that has only one dominant disease allele will develop the disorder. The chance of developing a disease in case of recessive inheritance is 25% and in case of dominant inheritance is 50%. For example, Sickle-cell disease is inherited in a recessive manner. Both parents carry the mutations on haemoglobin beta (HBB) on only one gene, the disease is not expressed in any parent. However, the chance that their child carries both recessive genes is 25% and in such case, the child will express the symptoms. The haemoglobin cells is in crescent shapes and being blocked in small capillaries, which results in the lack of oxygen and nutrition then organ's death[13][14].

In many other cases, parents may have perfectly healthy genes but their children can develop a rare genetic defect by a sporadic mechanism. Rett syndrome, a progressive neurodevelopmental disorder, is caused by a sporadic mutation of MECP2 gene. A vast majority of cases of Rett syndrome is not inherited and happens randomly. The parent's chromosomes are normal but the abnormal genes happen in one parent's reproduction cells. Only 1% of recorded cases is inherited or pass to the next generation[15][16].

### **b. Other causes**

Besides the rare genetics rare disorders, other rare diseases can be degenerative or proliferative disorders, resulted from an infection or environmental exposure.

Creutzfeldt Jakob disease (CJD) is known as an extremely rare degenerative brain disorder. 90% of reported cases appear randomly with no reason. 10% of patients may have a genetic predisposition from parents. It is believed that CJD is caused by an abnormal change of shape of a human prion protein PrP<sup>c</sup> to PrP<sup>sc</sup>. This change of shape leads to the degeneration and loss of brain cells progressively. In 1996, the British government announced that there is a link between Bovine Spongiform Encephalopathy (ingestion of infection beef) and CJD[17].

Whipple Disease causes a malabsorption of intestine and spreads to other parts of the body like the heart, lung, brain or eyes. The origin of this disease is believed the infection of Tropheryma Whippelii bacteria. The typical symptoms of this disease are abdominal pain, digestive problems, which lead to anaemia. In a severe form, when the bacteria reach the central nervous system or the heart (in rarer cases), patients may have neurological or cardiovascular problems such as hearing loss, vision damage or heart failure[18].

Some environmental exposure can also cause rare intoxications, for example, heavy metal poisoning (which is classed as rare diseases according to National Organization for Rare Disorders (NORD)[19].

## **2. Prevalence and new cases**

Currently, there is no information about prevalence of rare diseases on global scale. We have Orphanet and NORD, who provide inventory of rare diseases respectively in Europe and America.

The information published on these two portals cannot be considered to be absolutely exact because of difficulties in collecting information about rare diseases. According to Orphanet, in many cases, the prevalence can be only estimated according to the epidemiologic studies conducted in the hospitals with great prevalence of rare diseases. Many patients may suffer the same disease but have never been diagnosed then never have been documented[9].

## **C. Diagnosis, Prevention and treatment of rare diseases**

### **1. Diagnosis**

Among 8000 rare diseases listed on Orphanet and NORD, many diseases' causes and symptoms remain unknown. As a result, the diagnosis for rare diseases is still limited. Due to the lack of understanding about rare diseases, it may take years to have a correct diagnosis after first symptoms appear and the possibility of a correct diagnosis for a rare disease depends on clinical practices of physicians, whether the physicians are up to date to information about rare diseases.

Usually, a diagnosis starts with a classical routine: physical examination, information collection about patient's and family's medical history, laboratory tests. The results of laboratory tests together with the symptoms allow the physician to come to a primary diagnosis. However, for a same rare disorder, the symptoms can vary from one patient to another. Many patients with atypical symptoms make the diagnosis nearly impossible or much longer than usual. As a result, patients with rare diseases suffer from delayed diagnosis or even misdiagnoses. A late diagnosis can cause reduce significantly the surviving chance of patients. According to a study conducted by Shire about impacts of rare diseases on patients and medical community, it takes on average 7.6 years in the US and 5.6 years in the US for a patient to receive a proper diagnosis. Before getting a correct diagnosis, a typical patient may have to make visits up to 8 physicians and receives 2-3 misdiagnoses. [20]

As 80% of rare diseases have genetic origins, many patients are diagnosed with a rare disease only after genetic tests, however, genetic tests can be available in several locations, are usually very expensive and not covered by common health insurances.

Nowadays, many patient organizations and health authorities start to provide more education to physicians about rare diseases in order to increase the chance of correct diagnosis in the future.

Genetic screening is also advised for family members of patients with rare diseases so that the general knowledge about rare diseases can become more popular. On February 2018, Microsoft, Eurordis and Shire formed a Global Commission to accelerate the diagnosis for children with rare diseases. The aims of this commission is to improve the physicians' ability to detect the rare diseases to start the correct treatment as early as possible and to provide education and support for patients and families in order to have a better outcome for children with rare diseases. [21]

## **2. Prevention**

In order to prevent new cases of rare diseases, there are two preventive methods: primary and secondary prevention.

Primary prevention's aim is to prevent the diseases before it may occur by eliminating or reducing causal factors such as environmental exposure or infection. The common measures are to increase public immunization against infectious diseases by increasing the hygiene in daily activities and to avoid exposure to toxic agents. Another act of primary prevention for women during pregnancy is to take folic acid and to avoid any medicines that can cause malformation or defects in children. For some well-known rare diseases such as thalassemia, cystic fibrosis, a genetic screening is advised for couples before marriage or before pregnancy. A genetic screening permits to identify the carriers, to reduce the risk of having a child from both carrier parents and to increase the understanding about rare diseases in communities.

In case that a rare disease is already detected, secondary prevention is advised in order to minimize the impact of disease or the opportunity of spreading the disease. A new born genetic screening is an example for secondary prevention. Many health authorities have developed the new born screening (NBS) panel. The lists of diseases to be detected by this screening can be different from one country to another: the US panel can detect up to 30 disorders, Germany proposes 12 metabolic disorders, France screens for phenylketonuria only. This approach allows to identify the disorder before any symptoms appears, to reduce the burden of diagnostics and a better healthcare system for patients. [22]

## **3. Treatment**

There are different ranges of treatments for rare diseases, from curative, disease modifying or

symptom modifying.

Curative treatments for rare diseases are generally very rare. In many cases, there is no effective curative treatment, for example: rare poisoning (cyanide) or rare infection (Nontuberculous Mycobacterial Lung Disease). In some other cases, surgery or organ transplantation can be also considered as curative treatments. Surgery is often used when the disorder causes an anatomical defect. For child with craniofrontonasal dysplasia, after neurosurgeries and plastic surgeries, patients can have normal life with social and medical supports. For patients in advanced state of primary hyperoxaluria, a metabolic disorder that leads to kidney failure, a kidney transplant or a combination of liver-kidney transplant are usually considered as curative treatment. However, the effectiveness of such methods is controversial because of short and long term health problems and a long-life following up care. Surgery and transplant should be only used when the benefits clearly outweigh the risks and lifesaving for patients. [23]

Disease modifying and symptom treatment may or may not involve orphan drugs. Disease modifying is to delay the advancement or limit the harmful effects of the disease. For example, for Gaucher disease, a rare metabolic disorder that leads to a harmful accumulation of fat through the body, the standard treatment is the enzyme replacement therapy (ERT). The orphan drug Ceredase (alglucerase – injection) was approved by FDA in 1991 as treatment for Gaucher disease type I. However, a disease-modifying treatment can be effective for a form of disease may not work for other forms. [24]

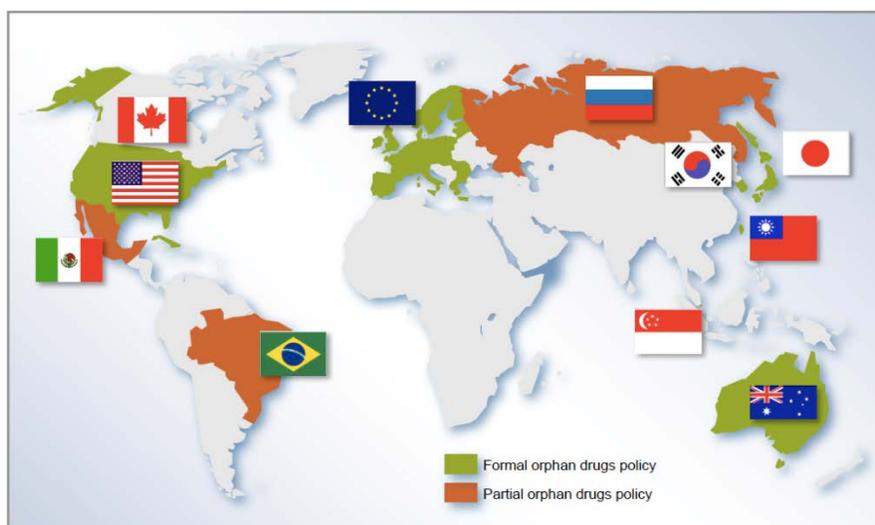
Symptom treatment focuses on relieving the symptoms and improving life-quality for patients with chronic diseases. A symptomatic treatment can be medication, nutritional agents, surgery or physical therapy. For many rare diseases, there is no curative or disease-modifying treatments and the treatment provided by physicians is only for symptoms and to prevent the complications of disease and to maintain a certain level of well-being of patients.

Along with the treatments, lifestyle changing and patient education play an important role in treatment therapies. For example, for patients with xeroderma pigmentosa, avoiding direct exposure to sunlight (UV), using sun cream and vitamin D can help to prevent DNA damage and disease advancement. Patient education via different information channels can help to increase the understanding about the disease, therapeutic plan for both patients and family members. [25]

# PART III. LEGAL FRAMEWORK FOR RESEARCH AND DEVELOPMENT OF ORPHAN DRUGS AROUND THE WORLD

## 1. Regulatory Landscape for Orphan Drugs worldwide

On 4<sup>th</sup> January 1983, the Orphan Drug Act came into law in the United States, as the first legislation on orphan drugs development in the world. The act was created in order to set up a regulatory recommendation for the development of medical treatment for rare diseases from definition and designation of orphan drug status, protection of drugs under development as well as economic incentives for the enterprises. Since 1983, more and more countries have developed their own legal framework for orphan drug research and development activities: Japan with Pharmaceutical Affairs Law (PAL), where rare diseases and orphan drugs were first defined in 1993, Australia with Orphan Drug Policy in 1998, the regulation (EC) No. 141/2000 and Rare Disease Control and Orphan Drug Act in Europe and Taiwan respectively in 2000, South Korea with Orphan Drugs guideline in 2003 etc



*Figure 1. World map of Orphan Drug Policy [26]*

Orphan drug policies and regulations have been introduced in nearly 40 countries around the world, in order to identify the challenges, to set up a regulatory requirement and to support the development of orphan drugs by the incentives such as tax credits, marketing exclusivity, free scientific advices, accelerated approval process or pre-licensing or off label programs. The patient

advocacy was one of the important factors that the US Orphan Drug Act and EU Regulation (CE) No.141/2000 elaborated. The most well-known international patient associations are European Organization for Rare Diseases (EURODIS) and National Organization for Rare Disorders (NORD) in the US. These patient associations aim to provide a better information and education to the healthcare professionals, patients and their surroundings about rare diseases and treatments.

Some countries develop their own national rare disease plan, which define the access to treatment, information, research stimulation or patient advocacy. France is the first European country who builds a national plan for rare diseases. The first national rare disease plan 2004-2008 was set up with ten strategic priorities to “ensure equity in the access to diagnostic, treatment and provision of care for people suffering from a rare disease”. The second national plan 2009-2014 was elaborated in the perspective of improving access to diagnostics and treatment for patients, encouraging the research for the sponsors and boosting international cooperation in orphan drug and rare diseases field. [26][27]

## **2. Orphan drug designation**

### **a. The United States**

The US is the first country who elaborated a legal framework about rare diseases and orphan drugs in Orphan Drugs Act in 1983. However, the definition of rare diseases was not clearly defined in this act. After the amendment in 1984, the definition of rare diseases was qualified with an **orphan subset** of less than 200 000 people in the US. As a result, sponsor or manufacturer can ask to designate the \*Orphan Status\* for the products that are intended for safe and effective treatment, diagnosis and prevention of rare diseases that affect fewer than 200 000 people in US or affect more than 200 000 people but not expected to recover the costs of developing and marketing a treatment drug. The request can be applied for an unapproved drug or a new use of a marketed drug, however, a product can be still approved as orphan drug without having orphan drug designation and not all products with orphan drugs designations will be approved as orphan drug. [28]

According to 21 Code Federal Regulations Part 316-Orphan Drugs, all requests for Orphan Drugs should be addressed to Office of Orphan Products Development (OOPD), Food and Drug Administration (FDA). The sponsor can submit the request during the pre-clinical or clinical

development without an IND status (Investigational New Drug) providing:

- Statement that the sponsor requests orphan drug designation for the rare diseases
- Identify the sponsor and the drug
- Justify the necessity of the drug by describing the rare disease and the proposed use of the drug
- Provides description of the drug in detail and justify the scientific rationale for the use of the drug
- If same drug has been approved for the same disease, explanation of the clinical superiority of the new drug
- If the request is for an orphan subset of a common disease, explain why some property of the drug or biologic would limit use of the product to the subset
- Summary the regulatory status and marketing history
- Documentation on the disease: Prevalence or no reasonable expectation that costs of research and development for such disease can be recovered by sales.

The evaluation of orphan drug designation is conducted basing on three elements: the characteristics of the disease (what is the disease?), the rarity of the disease (is it rare?) and the scientific rationale that the sponsor demonstrates to prevent/treat the disease. In order to prove the scientific rationale of the drug, the sponsor needs to provide the information about the effectiveness of the drug from clinical data, or animal models or in vitro data for the disease that no adequate animal model possible.

After 90 days of review, the sponsor receives a designation letter (designation granted) or a deficiency letter (refuse). Every year until the approval for commercialisation, the sponsor is required to submit annual report providing a review of ongoing clinical trials, a description of the investigation plan for the coming year and any anticipated or current problems during the research and development process that potentially impact the designation status. [7][29]

## **b. EU**

The regulation (EC) No.141/2000 was published in Official Journal of the European Communities in 2000 in order to set a framework for medicinal products as treatment of rare diseases. The regulation also establishes the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA) to be in charge of evaluation of treatments for rare diseases. Since 2009, no notification of intent for an orphan drug designation is need. A sponsor can submit the application to COMP without notice. The submission deadlines are available on EMA website. It is advisable that the application should be sent a few days before the deadline to give more time for validation process. If the medicinal product is an Advanced Therapeutic Medicinal Product (ATMP), the sponsor should submit to the Committee for Advanced Therapies (CAT) for classification and naming before submitting the orphan designation to COM.

The sponsor also has a possibility to ask for a pre-submission meeting in person or via teleconference with EMA experts two months before the submission date. This pre-submission meeting is highly recommended by EMA and appreciated by many sponsors. One week before the pre-submission meeting date, the sponsor should send the draft application via an account on Eudralink platform. During the pre-submission meeting, the sponsor should make a presentation on the designation application focusing on the following points:

- Condition and scope of the application
- Description of the active substance (mode of action, in vitro, in vivo or non-clinical and clinical supporting data if available)
- Nature of the disease
- Benefit in compared to other exiting treatments
- Intention to submit the designation to other agencies (US or Japan)

During the pre-submission meeting, the application form and the scientific of the designation application can be also checked in term of quality. The sponsor is required to take minute of the meeting and send to EMA one week after the meeting in order to obtain the amended minute

from EMA.

The evaluation team of the application is consisted of one COMP member and one EMA member for each application. The submission package should include the following documents:

- Cover letter
- Application form
- Scientific sections of application
- Proof of establishment of sponsor in EU (physical address and name of contact person)
- Letter of authorisation for person who acts on behalf of sponsor during procedure
- Translation of name and proposed indications of products in official languages in EU, Icelandic and Norwegian
- Bibliography.

The application form and scientific sections (A to E) are available on EMA website. The scientific sections (A to E) are to provide scientific support data to the orphan designation application. They focus on five following points:

- Description of the condition
- Prevalence of condition
- Potential for return on R&D investment
- Existing methods for diagnostic, prevention or treatment of condition
- Description of the stage of development.

These are essential points to be evaluated in the application by evaluators from COMP and EMA. Once the submission is received by EMA, the submission will be validated during one week. After one week, a validation letter will be issued before starting the evaluation procedure. The

procedure is 90-day long with no clock stop, starting from the day that the submission is validated.

In Europe, when a sponsor submits a request for an orphan drug designation, COMP examines the application by:

- Nature of the condition (life-threatening or debilitating)
- Medical plausibility of proposed orphan indication
- Prevalence of the condition in European Union (EU) is not more than five in 10.000 or that it is unlikely that without incentives, the medicinal product will generate a sufficient return for the R&D investment for the sponsor.
- No satisfactory method of diagnosis, prevention or treatment exists or the product will provide a more significant benefit to patients than existing methods.

During the evaluation procedure, the appointed experts will gather the information about the disease and circulate the scientific data among other experts in COMP and EMA. The application will be discussed during the COMP meeting. If questions are raised, a list of question will be sent to applicant three days after the meeting and the applicant will be asked to present the responses in written form or in an oral meeting with the experts. Before day 90, COMP opinion will be adopted. If the outcome is negative, the applicant will be informed and has a possibility to withdraw the application before the official announcement. Once the official COMP opinion is issued in COMP monthly report, the applicant has 90 days to appeal the negative opinion. 30 days after the reception of the sponsor appeal, the final decision of COMP will be published in EMA website.

In case of favourable opinion, the COMP opinion will be sent to European Commission and the Commission decision will be granted within 30 days. The designated product will be registered in Community Register of Orphan Medicinal Products. [30]

EMA strongly recommend the applicants to submit in parallel the orphan designation to FDA (US) and MHLW (Japan) if the product is not designated in these two countries. A common

submission EMA/FDA is possible by using a EMA/FDA application instead of EMA application in submission dossier.

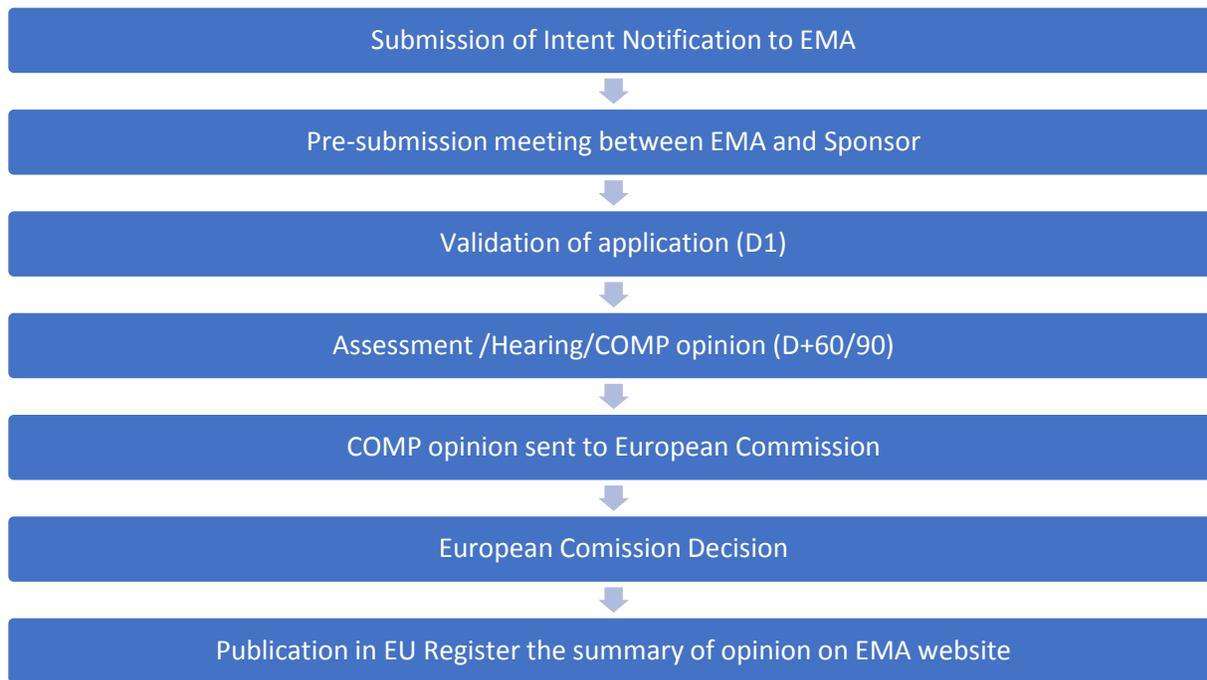


Figure 2. Summary of orphan designation in flow chart in EU[31]

	2000 2005	2006 2010	2011 2015	2016	2017	2018	<b>Total</b>
Applications submitted	548	686	1151	329	260	236	3210
Positive COMP Opinions	348	500	759	220	144	163	2134
Negative COMP Opinions	8	6	7	2	2	3	28
EC Designations	343	485	768	209	147	169	2121
Withdrawals after submission	150	144	313	77	100	92	876

Figure 3. Number of Application for Orphan Drug Designation in Europe from 2000 to 2018 [32]

### c. Japan

In Japan, the legislation about orphan drugs was first introduced and came into force in Pharmaceutical Affairs Law (PAL) in 1993. According to Minister of Health, Labour and Welfare (MHLW). The orphan drug legislation in Japan has similarities with US system, however, in Japan, orphan designation covers not only medicines but also devices and vaccines. In the revised version in 2014 of PAL, chapter 15, article 77-2 to 77-7 were dedicated to the designation of orphan drugs, orphan medical devices and cellular and tissue-based orphan products in Japan. The application will be evaluated by Pharmaceutical and Medical Devices Agency (PMDA) and Pharmaceutical Affairs and Food Sanitation Council (PAFSC). Based on the assessment of PMDA and PAFSC, the status will be granted or declined by MHLW.

A medicinal product will be designated **orphan status** if it fulfils the following conditions:

- Patient population: less than 50.000 patients in Japan
- Medical needs: there is no alternative medical treatment and the proposed product has a higher efficacy or safety in compared to existing treatments.
- Development possibility: the applicant should be able to present a rational development plan for the targeted disease with non-clinical and clinical data.

Similar to European procedure, an applicant can request for a designation consultation (pre-submission meeting) with MHLW anytime. An application for the consultation can be sent by post or fax to MHLW together with the summary of the product. The consultation is held by Evaluation and Licensing Division (LED) in MHLW.

For the designation application, the applicant can send by post an application, which is available on MHLW website, together with a scientific attachment providing data on:

- Patient population: number of targeted patients in Japan
- Medical needs: data on disease and current status of treatment for this disease
- Theoretical rationale for the use of product: a draft dossier for application of marketing

authorisation

- Origin and history of discovery and usage condition in foreign countries if exist
  - Manufacturing methods and stability
  - Pharmacological data
  - Pharmacodynamics data
  - Toxicology data
  - Clinical data if available
- Development plan: current development status, expected test items, duration of the study and necessary expenses.
  - Preparation of summary of the product for the Committee meetings and publication

The application will be received by LED of MHLW. MHLW will transfer the data to PMDA for a preliminary review of the application. If the designation is feasible, MHLW will consult PAFSC. A designation will be granted by MHLW only if PAFSC approves the request. The result will be published on MHLW Ministerial Notification. [33]

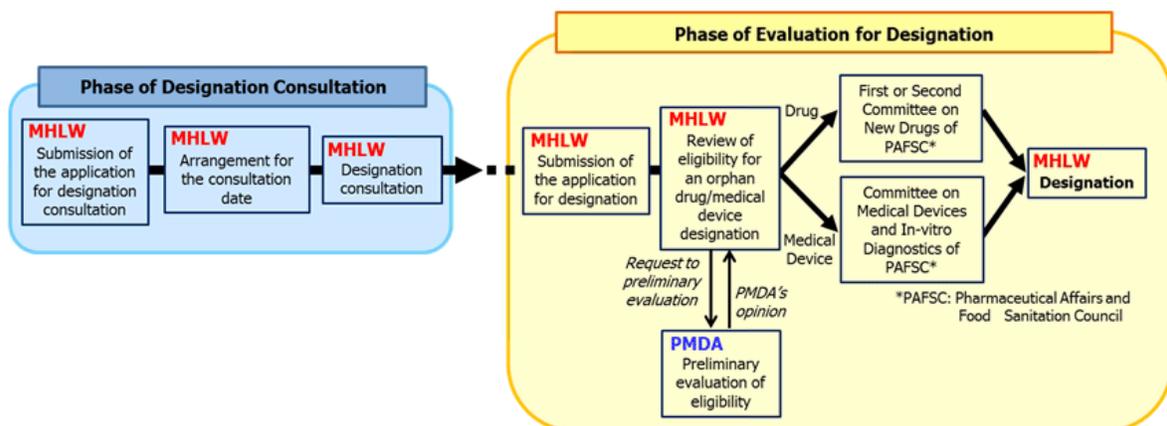


Figure 4. Orphan Drug Designation Evaluation Process in Japan[34]

### **3. Regulatory Requirements for Orphan Drugs Development**

#### **a. Early Discovery Stage**

The discovery of a new orphan drug is usually initiated by an unmet medical need and understanding the nature of the disease is a useful tool for the start of the development. The development begins with the research in the laboratory in order to identify the mechanism of the disease at molecular scale.

As most of rare diseases have genetic origins, many different gene studies can be adopted to map the genetic pathogenesis such as: tradition genetic studies in order to identify the defect single gene, study of modifier genes and epigenetics to understand better about the primary and secondary expression of the gene with different modifier genes. This study allows the researchers to discover the biomarkers of the disease and identify the therapeutic targets that a drug may act on. Biomarkers play important roles in diagnostic, endpoints in non-clinical and clinical trials to evaluate the disease and the effect of the treatment. A biomarker can be genomics, proteomics or metabolomics. Following the ICH E15 and E16 about the definition and qualification of biomarkers, EMA has prepared their own guideline to standardize the critical attributes of biomarkers, which are:

- Analytical validity: a biomarker should enable a clear difference between a normal and an altered status, with or without treatment.
- Clinical validity: a biomarker should provide an accurate reflect the features of a disease or a treatment without being influenced by circumstantial factors like age, sex, diet, stress etc. A biomarker should be specific, sensitive and accurate at the same time.
- Clinical utility: an ideal biomarker should enable to predict the development/manifestation of a disease in a given circumstance
- Non-invasiveness: a biomarker should be easy accessed by body fluids or images.
- Feasibility/Time and cost effectiveness: a biomarker should be easy and quick to identify and measure with existing methods and not so costly.

The identification of translational biomarkers allows developing the discovery strategies. The discovery strategies will result in identification of the lead molecule, which has an ideal action on the translational biomarkers. The molecule will be optimized to obtain an optimal therapeutic action in both biopharmaceutical and safety level. At this point of the research, the drug discovery is finished. The drug candidate that can prove a certain level of efficiency and safety can enter to preclinical phase in in vitro or in animal models. [35] [36]

### **b. Pre-clinical Trial**

Nonclinical trials are designed and conducted in order to get a deeper understanding about characteristics of the candidate compound and assure that it is sufficiently safe and efficient to conduct the trials on human.

Guidance M3(R2) on Nonclinical Safety Studies For The Conduct Of Human Clinical Trials And Marketing Authorization For Pharmaceuticals was created and implemented in by different Health Authorities (Europe, Japan, US, Canada and Switzerland)[37, p. 2] in order to set the common regulation about conducting preclinical trials for any new pharmaceuticals. Any trials conducted on animals should follow the 3R rule:

- **Reduce** (reduce the amount of animal used in the trials)
- **Refine** (refine the experimental conditions in order to reduce the suffering and improve the wellbeing of animals)
- **Replace** (replace the animal experiments by in vitro experiments whenever possible).

Usually, the nonclinical trials can be conducted on in vitro/in vivo or on animal models and should include following studies:

#### **b1. Pharmacology studies**

Pharmacology studies can be divided into 3 categories:

##### **Primary and Secondary Pharmacology**

Primary pharmacology studies allow demonstrating primary actions of drug candidate on intended targets at cellular level. Primary pharmacology plays an important role in providing

Proof of Concept, the mechanism of action, the efficacy of the molecular in expected therapeutic indication.

Secondary pharmacology studies are useful to understand the action of molecular in unexpected targets such as binding to unexpected receptors or in receptors in undesired organs, which may lead to a new indication or toxicities.

### **Safety Pharmacology**

Since 2000, the guideline ICH S7 – Safety Pharmacology Studies for Human Pharmaceuticals was implemented in different countries to harmonize the pharmacology studies in preclinical trial phase of drug development. According to this guideline, the safety pharmacology studies can be conducted in both in vivo and vitro. The objective of this study is to establish the dose-response relationship of the drug candidate by identifying possible toxic activities of the drug candidate in different organs. It is recommended to test the effect of the drug candidate in several vital systems: Central Nervous System, Cardiovascular System and Respiratory System (Safety Pharmacology Core Battery). [38]

#### **b2. Pharmacokinetics-Toxicokinetic**

Pharmacokinetic studies are necessary to understand the transformation of the molecule after being administered. These studies allow predicting how the drug is transformed from absorption, distribution, metabolism and elimination inside a living body. Important factors of the drug profile can be identified such as toxic metabolic, drug interaction with other drugs or physiological compounds (plasma proteins, hepatic cytochromes, digestive enzymes). Toxicokinetic studies are conducted to understand the toxic profiles at high doses. Pharmacokinetics and toxicokinetic studies enable to determine the endpoints for clinical trials such as C<sub>max</sub> and T<sub>max</sub>(maximum serum concentration of the drug after a fixed period of time), clearance, volume of distribution, bioavailability. [39]

#### **b3. Toxicology studies**

Beside safety pharmacology and toxico-kinetics studies, single and repeat-dose toxicology studies are conducted to obtain information about dose-ranging effects in human and essential to support the marketing authorisation dossier. Acute toxicity tests should be conducted in two

mammalian species by both intended administration mode and parental route. Repeat-dose testing should be conducted in two different species (rodent and non-rodent). The duration of the repeat dose studies depends on the duration of the treatment. [39]



*Figure 5. Duration of repeat dose studies in rodent and non-rodent species[39]*

In case the clinical trials are addressed to paediatric population and the maximum duration are more than 6 months, the minimum of repeat dose testes should be 6 months in rodents and 9 months in non-rodents. If developmental issued are identified in target organs, long term toxicity testing in juvenile animals may be needed in some cases.

#### **b4. Preclinical Safety Studies in Bio-Pharmaceuticals**

In case the drug candidate is biotechnology-derived, the guideline ICH S6 (R1) Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals was developed to propose a basic legal framework for preclinical trials. This guideline can be applied for characterized cells via different expression systems, products produced from recombinant DNA (proteins, peptides, vaccines etc). [40]

The variety of biotechnology-derived products resulted from the production process such as the rate of impurities or contaminants may be a great risk for safety issues. Because of the specificity the manufacturing process, asking for identical products used in both preclinical and clinical trials are impossible. It is recommended that the products used in preclinical trials should be similar or as much comparable to products proposed to use in clinical trials as possible. The similarities should be evaluated based on the biochemical and biochemical characteristics of the

product.

The preclinical trials can be conducted in both in vitro and in vivo conditions in order to obtain a better understanding and extrapolating results in pharmacological, pharmacokinetics and toxicology of the product in human body. For in vitro studies, human cells and cell lines can be useful to demonstrate the efficacy and safety of the drug candidate in vivo and human trials. The in vitro studies would place a significant role to prove safety of the drug when no relevant animal models are available.

The animal models used in preclinical trials should be chosen based on the relevant biological profiles, age, physiological situation, delivery mode. The relevant animal models are the species that express the receptor or epitope of the candidate molecule. Monkeys are usually used for testing the fully human derived products if the product is addressed for repeat dosage if no lower species are physiologically relevant to the disease. Because of the rarity of the disease, it is difficult to find the animal species with the disease's gene expression in nature. In such case, transgenic animals expressing human receptors or homologous proteins will be used and a short-term toxicology studies (14 days) in rodent species could be accepted in registration dossier. Normally, two types of species should be included in safety non clinical trials. Rodents and rabbits are the most common species to be used in preclinical trials. However, most biopharmaceutical-derived products require toxicology studies in non-human primates to prove the efficacy and safety of the drug. Utilizing one single species can be used if justification is rational. For single dose and repeat dose toxicity studies, biopharmaceuticals have natural origins; therefore, the transformation pathway is well understood. The pharmacokinetics and pharmacodynamics data of preclinical trials for biopharmaceuticals are critical because the efficacy and safety are mainly based on this information. Many biopharmaceuticals are toxic because of the exaggerated pharmacodynamics action and the possibility of inducing immunogenic reaction. Identifying the undesired pharmacodynamics mechanism and product-specific antibodies in animals helps to predict the unwanted actions of drug in human body. However, the reactions in animals can be different with those in human. These data remain predictive but not indicative for human trials. Safety pharmacology (core battery tests), genotoxicity and carcinogenicity studies may not be necessary in biopharmaceuticals, unless the safety pharmacology results in vitro are strongly evident to lead to further studies[40].

### **c. Clinical Trial**

In 1996, the first document about regulations applied to conduction of clinical trial was elaborated and approved by ICH Guideline For Good Clinical Practice E6 (R1)) [41]. However, because of the small population of patients, the heterogeneity of clinical and biological signs and the poor understanding of the pharmacology/pharmaco-pathology, it is much harder for clinical trials conducted on rare diseases to prove the efficacy and safety of the drug candidate under the same regulations applied for non-rare diseases. As the result, EMA and FDA elaborated the guidelines dedicating for clinical trials conducted in small populations to give approaches specialized for rare diseases[42]. Regardless orphan or non-orphan drugs, the efficacy and safety of new drug will be evaluated with the same standard as for non-orphan drugs. There is no automatic deviation for orphan drug clinical trials. Any flexibility should be explained thoroughly by the applicant and will be considered case by case by the authorities. In comparison between orphan clinical trials and non-orphan clinical trials, the duration and other features of the trial such as randomization, blinding or placebo control are stated to be the similar.

The evidence of efficacy and safety can be provided in different approaches: randomized controlled trials, observational studies, case reports or opinions of experts in this domain. Randomized controlled trials are the most preferable if feasible. Otherwise, controlled studies are considered to bring more reliable information than non-controlled studies. Case studies may be also acceptable in some cases but patient treatment and information collection should be conducted under GCP standard and further studies after marketing authorization may be required. For rare diseases, the mechanism of pathology is usually unclear; therefore, it is not easy to demonstrate the pharmacology and the efficacy of the drug candidate. Clinical trials should be designed based on the information obtained from pre-clinical trials, especially for dosing and administration route, pharmacodynamics and pharmacokinetics measurement. For the products that the pharmacodynamics and pharmacokinetics are well known, it is sufficient to accept the result comparison among the patients for benefit-risk evaluation. Especially for extreme rare diseases, the contribution of information from patient register from the early stage of clinical trials is very important to have a better benefit risk assessment.

For rare disease treatment, choice of endpoints is essential in clinical trials design. The endpoints for clinical trial can be a complete cure for disease or can be just symptom relief and survival. The endpoints for clinical trials in small populations can be time to disease progression,

clinical endpoint or symptom relief or a surrogate endpoint. Time to disease progression or disease remission is usually used as an intermediate endpoint and requires an evaluation of disease progression in long term. A clinical endpoint is used when this clinical symptom has a significant impact on the well-being of patients. Usually, if absence of clinical symptoms is considered as clinical endpoints, further treatment – dependent information needs to be provided to prove the causal relation between the results and the drug efficacy. However, in practice, the choice of an appropriate endpoint can be very challenging because of the uncertainty in the disease progression as well as the test treatment. The life expectancy and the number of participants in clinical trials can vary unexpectedly; therefore, it can cause many difficulties in determining clinical endpoint or disease progression. In rare diseases, a surrogate endpoint using a validated biomarker can be considered if a strong foundation of epidemiology, pathophysiology of the disease is available. A surrogate endpoint should be chosen based on its relation with the clinical symptom development or other existing therapies. However, using only surrogate endpoints is rarely accepted to as adequate proof of the efficacy and safety of a drug. Further information about epidemiology, patient registers and follow up studies post approval will be necessary to evaluate the benefit risk and long term effect of the treatment. [43]

It is not unusual that when a drug candidate comes to clinical trial phase, there is no equivalent treatment to be used as a controlled group. When there is no existing treatment, placebo can be used as a comparator. This method raises a lot of ethical questions, when most of patients in rare diseases are children or have very low life expectancy. In many other cases, a controlled group can be a group treated by standard care. For example, when doing the clinical trials for sudden hearing loss syndrome, the patient groups treated with current medical approaches such as: corticoids, oxygen therapies, antibiotics are used as comparator arm. Two approaches are possible for a controlled group: internal controls or external controls. Internal controlled group is more preferable as the problems related to medical histories can be well taken into account at the early stage of designing a trial. A clinical trial without a controlled group can be accepted if the mechanism of the disorder is very well understood.

In classical clinical trial, phase 1(First in Man) is conducted to test the safety of the drug candidate in healthy volunteers to determine the dose limit toxicity. However, it is very popular that in rare disease clinical trials, many applicants use an innovative design: combine the phase 1

and phase 2 by studying directly on patients instead of healthy volunteers. Patients are treated with different dosages are strictly followed to report any events on pharmacodynamics, pharmacokinetics and adverse reactions. Once the phase 1-2 trial can prove the efficacy and safety of the drug candidate, the applicant may apply for Orphan Drug Designation.

#### **d. Paediatric Investigation plan**

In USA, there are two legislations applied on the development of medicines addressed to children:

- PREA: Paediatric Research Equity Act, which is obligatory to submit at the moment of application for marketing authorization. [44]
- BPCA: Best Pharmaceuticals for Children Act: which grants 6 months extra for market exclusivity [44]

In 2006 in Europe, Regulation (EC) No 1901/2006 as amended by Regulation (EC) No 1902/2006 – the paediatric regulation was elaborated and used as the base of regulations of development for paediatric population. [45]

Paediatric Investigation Plan is a development plan elaborated to ensure that the information about the use of the drug candidate on children is obtained in a safe way and to support the marketing authorization in children population. All the marketing authorization applications for new medicines are now required to submit the PIP, except the case that a deferral or a waiver is granted.

Nowadays, when the application of marketing authorization can be done in a common portal between Europe and USA, the applicant tends to apply one PIP that can be applied in both markets.

A PIP will contain the following information:

- Rationalization the use of the drug on different ages of children. If the drug is targeted in only one or several subsets of ages, further justification on epidemiology data is required to justify the rationalization of the applicant.

- An Overview of disease: nature of disease, existing methods of diagnosis and treatment in showing the need of development a treatment for children.
- An overview of the medicines: chemistry - formulation data, non-clinical and clinical data.
- A proposed development plan for formulation or further non clinical, clinical trials in children.

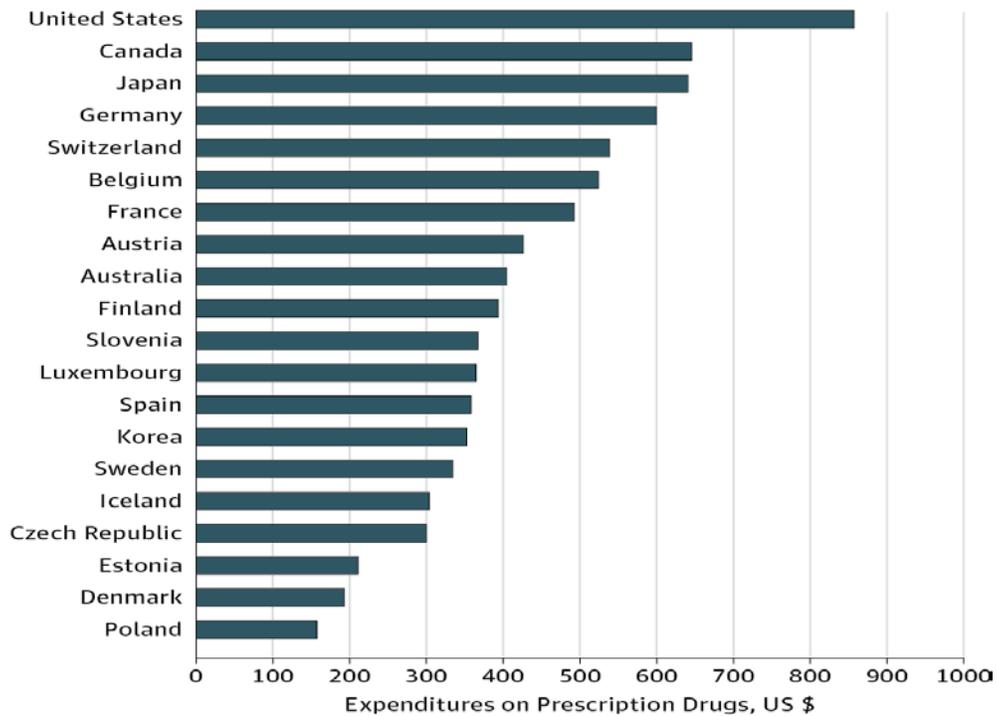
The application should be submitted to the Paediatric Committee of European Medicines Agency (PDCO). The evaluation time may take up to 9-10 month. The PIP should be submitted before the end of the pharmacokinetics trials on human and is required to be presented before the application for marketing authorization so that there is space for further discussion after PDCO evaluation if needed. [46]

#### **4. Early patient access, pricing and reimbursement**

##### **a. USA**

##### **a1. Pricing and reimbursement**

Unlike many other developed countries in the world, there is no price negotiation between the MAH and a healthcare technical body in USA. The MAH can set their own price, based on their R&D cost, as long as the society can still tolerate the price. According to data provided by Organisation for Economic Cooperation and Development (OECD) in 2013, the United State has the highest spending on prescription pharmaceuticals, following by Canada, Japan and Germany[47].



*Figure 6. Expenditures on Prescription drugs in US dollars [48]*

In the United States, the annual cost for an orphan drug can range from less than 6000 dollars to more than 600.000 dollars. It is estimated that the median annual patient cost for a treatment of rare disease in 2017 is over 46.000 dollars. However, the number of target patients is not correlated with the price of an orphan drug. More than 30% of prescribed orphan drugs cost between 6.000 to 50.000 dollars. The treatments that cost more than 500.000 dollars per year represent only 1.2% of the total amount of prescribed orphan drugs[48].

In the United States, the patients undergoing rare diseases treatments are covered by two public regimes: Medicare and Medicaid, based on age (over 65 years old) or criteria for Social Security Disability Insurance (SSDI).

### **Medicare and Medicaid**

Medicare was created to cover patients over the age of 65 in all income or health status. Besides, patients who qualify for SSDI can be also covered by Medicare if they apply for SSDI, who's the evaluation time can last up to 2 years. However, the evaluation process can be exempted for patients in specific conditions, especially for some rare diseases (amyotrophic lateral sclerosis,

children and adults suffering end-stage renal disease etc). In 2010, this exemption list included 38 rare diseases.

Medicare is divided into four parts:

Part A: Hospitalisation insurance

Part B: Supplementary medical insurance for physician and other services

Part C: Medicare Advantage Program, which allows beneficiaries to apply for private health plans

Part D: Outpatients prescription drug benefice.

Most patients treated by orphan drugs are covered by part D of Medicare policy. For drugs administered by physicians in their office may benefit Part B and be reimbursed up to 80% of medical cost.

Medicaid is a joint federal-state program to provide reimbursement based on income of applicants, especially low income individuals such as low income parents, low income or disabled patients) regardless their ages (over or under 65).

The Centres for Medicare and Medicaid Services (CMS) choose the reimbursement drugs based on two criteria:

- Designation as orphan drugs and approved by the DFA for the treatment of more than 1 orphan conditions
- Listed in the current US pharmacopeia Drug Quality and Information only for orphan indication, with no other approved indication or off label use.

This policy is created based on the fact that currently many orphan drugs are developed as indication extension, based on an existing drug with a non-orphan indication. Because of this one-indication orphan drug policy, some orphan drugs such as botulinum toxin type A (Botox) is not listed because it generates more incomes in cosmetics than in treatment of dystonia.

The orphan drugs that are not on Single-indication list, are covered by these two public regimes at various rates. It is estimated that, the annual Out of Pocket cost for each patient covered by part D is 5.700 dollars[22].

### **Private health plans in the US**

It is calculated that from 2008, private health plans in the US cover more than 65% of under 65 patients. Being covered by both public regime and private regime becomes very popular especially for employer-sponsored plans. Because of high cost treatment, only a small number of private health insurers can afford the out-of-pocket costs. For instance, for a patient who received 2 injections of Myozyme per month for Pompe diseases, the annual cost can be up to More than 300.000 dollars per year and if any complication or serious side effects come up, the hospitalisation fee can be up to more than 1 million dollars easily. As a result, as of 2010, the Affordable Health Care act prohibited private health insurers to limit the reimbursement time based on the value of coverage or to cancel the coverage because of the severity development of patient's health[49].

### **Patient-Assistance program from Patient Advocacy group and Manufacturers**

Many Patient-Assistance Programs were created by manufacturers themselves to provide more medical and financial help to patients who has no coverage such as: Genzyme Cooperation, Shire program etc. these programs allow their products to continue to be on the market. The assistance program may include: supply of treatment for reduced or free cost for a certain period of time, assisting of co-payment for patients with insurances, providing information regarding other medical and financial aid.

Advocacy patient group such as the NORD also provides some similar programs to assist the treatment of certain rare diseases such as Hunter Syndrome, paroxysmal nocturnal hemoglobinuria etc[22].

### **a2. Compassionate use in US**

In US, Compassionate use is called Expanded Access to Investigational Drugs for treatment use. In October 2009, 21 Code Federal Regulation (CFR) part 312 sub-part A came into force and allowed to use an investigational drug as a treatment to patients under a program called Expanded

Access (EAP). In 2016, FDA elaborated a Guideline to give further instruction about implementing the regulation 21 CFR part 312 subpart A. ([44])

Expanded Access in US can be used for an unauthorized drug (withdrawn MA, ongoing clinical trial or waiting for MA). The purpose of expanded access is to increase the availability of innovative treatment to patients affected to seriously debilitating or life threatening diseases. Expanded access program is only allowed if the drug used in this program is subject of an application for a marketing authorisation.

There are three categories of Expanded Access Program (EAP) in US:

### **For individual patients**

There are two forms of an EAP addressed to individual patients:

- Individual patient INDs or single patient IND: this program can be requested by a physician to a single patient to FDA. The drug in request may be under development or an approved drug. In such case, the request will be considered as a new IND. The physician must wait for a 30 day period after submitting the request to FDA in order to start the treatment. The physician may refer to an existing IND to justify his demand if he obtains the permission from the sponsor of this IND.
- Individual patient expanded access protocol or single patient protocol: this program can be requested for an existing IND and submitted by the sponsor of this IND. Therefore, this protocol can be used as treatment for several patients at the same time. A 30 day period is not necessary in such case but the protocol needs to be submitted to FDA before the commencement of the treatment.

In both case, there is an access for an emergency use, where the submission and the authorisation can be done by telephone and the written submission must be sent to FDA within 15 days after the beginning of the treatment.

**For an intermediate size population of patients: the size of the population must be smaller than currently investigational program (clinical trials)**

In the guideline from FDA, it is not stated clearly how many patient populations may request for the same programs with the same indication. However, if the patients are under the same conditions and would like to benefit the treatment for the same indication, it is preferable to have one program. The number of patients included in the program is not indicated in the regulation but it should not exceed the number of patients in a large clinical trial.

The expanded excess program can be granted only if the medicine is currently NOT subject to a marketing authorisation. If an investigation drug is ongoing, the treatment IND or protocols should be requested.

A single patient expanded access program can be integrated into an intermediate size patient population in order to reduce the administrative work and increase the following up.

- Intermediate size patient population expanded access IND: this program is used for a group of patient, whose size is smaller than a typical treatment IND or Protocols and considered as a new IND. There is a period of 30 days from the reception at FDA level before the program can start.
- Intermediate size patient population expanded access protocol: this program is feasible for a product with an existing IND, submitted as a protocol by the sponsor of the existing IND. There is no 30-day period before the commencement of the treatment, but the protocol should be submitted to FDA before the treatment begins.

#### **For a treatment in large scale by IND treatment**

- Treatment IND: this program is applied for a large patient population and considered as a new IND. There is a 30-day period from the reception of request at FDA until the start of the program.
- Treatment protocol: this program is used when the drug in request is an existing IND and it should be submitted by the sponsor of this IND. There is a period of 30 days waiting from the reception of the request at FDA to the start of the program.

In three cases, there is an access for an emergency use, where the submission and the authorisation can be done by telephone and the written submission must be sent to FDA within 15

days after the beginning of the treatment[50].

Over the period from 2005 to 2014, FDA received more than 1000 applications per year. 99,7% requests were accepted; the others were granted after some modifications in protocols for a better security following up. Most of the applications received by FDA are for one single patient IND or protocols for both emergency and non-emergency use. The most demanded therapeutic areas are: antiviral products, transplant and ophthalmology, haematology and metabolism disorders[51].

## **b. EU – General strategies and some examples**

After being approved centrally by EMA, a novel orphan drug may have go through numerous steps to be commercialized in each registered country. It depends on national policy in each country to grant the access of the drug to patients, especially price and reimbursement negotiation and dispensation. Orphan drugs are only prescribed by some specialized physicians and the usage is strictly in hospitals.

### **b1. Pricing and reimbursement**

Regardless the centralized registration procedure, the price and reimbursement are negotiated at national level. The pricing and reimbursement policy is constructed in order to balance between the honour for medical innovation, substantial national healthcare budget and equitable access to patients.

It is common among countries that the value of a new orphan drug is evaluated by a health technology assessment, based on the nature of the disease (rarity and severity), current alternative treatments, evidence for security and effectiveness of the treatment, technology innovation, and budget impact, social and legal issues. However, how these criteria are valued is different in each country. Therefore, there is a great variety in pricing and reimbursement of orphan drugs in Europe. Each country may have a different policy in determining the value of orphan drugs. The pricing and reimbursement policy reflects national society's point of view about how their national health care budget should be used. According to a study conducted in 18 European countries in 2011, the annual patient cost for a rare disease treatment is around 32.000 euros on average and can rise up to more than 400.000 euro per year. Moreover, it is always challenging to justify the cost effectiveness ratio of a new orphan drug because of the low prevalence, less

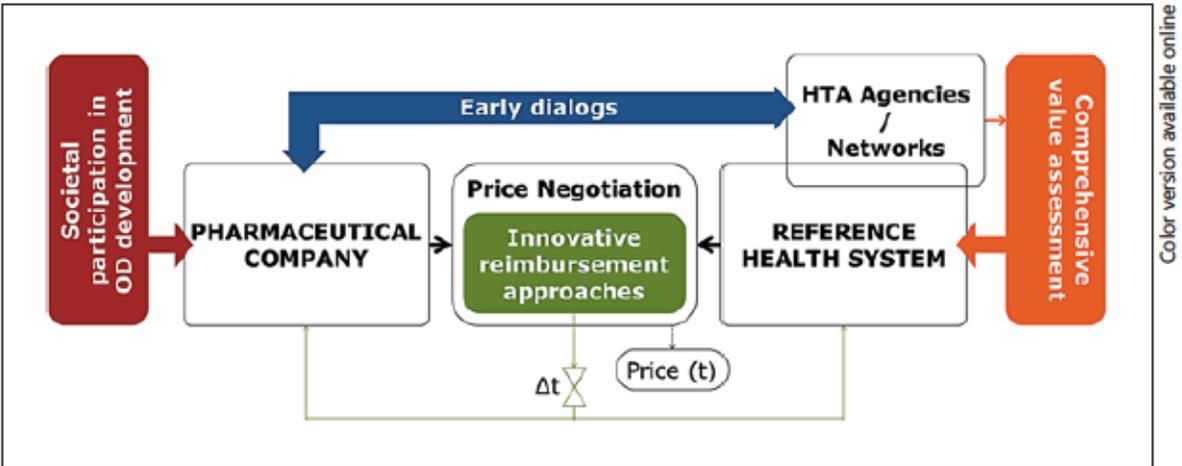
extensive clinical trials and absence of comparative treatment. Hence, it becomes controversial whether orphan drugs should be funded or not. When a new orphan drug comes into market with high price and no or low reimbursement, patient access will be restricted and the pharmaceutical companies risk to be no able to cover their development cost.

Some countries such as France and Sweden may value vertical equity. The citizens have strong sense for equal treatment for everyone, which means that all patients should be treated equally despite the minor prevalence and financial dispense. Other countries such as UK may value horizontal equity, which means the financial resources should be addressed to treat as much as patient as possible and national healthcare budget should not be used in priority for the rarity of the disease[52].

### **Reimbursed Price of Orphan Drugs:**

Currently, there are four strategies for orphan drug pricing and reimbursement in many European countries:

- Adopting a comprehensive value assessment by considering the priority setting, involving stakeholders and value-based factors along the evaluation. Priority setting may be contradictory depending on stakeholders (pharmaceutical company, healthcare government, patients and public) or approaches (social, political, financial or ethical points of view. Usually, the health technology assessment utilizes only the cost-effectiveness ratio, based on number of life changing time by treated patient. However, it is recommended by European Union Committee of Experts on Rare Disease (EUCERD) that the HTA should adopt a multi criteria decision analysis (MCDA) method in order to integrate the points of view from different stakeholders with different interests and value. Based on this common method of evaluation, national HTA takes into account the specificities of their country for fixing a price and reimbursement rate for a new orphan drug[53].



Color version available online

Figure 7. Current concept to determine drug price[53]

- Early discussion between the stakeholders before starting phase III clinical trial: an early information exchange starting from orphan designation between the pharmaceutical companies, EMA, European network of Health Technology Assessments is encouraged by EUCERD. This approach will allow relevant stakeholders to share a common understanding about the drug development, regulatory requirements as well as public health expectation pre and post marketing authorization; therefore facilitate the consensus for pricing and reimbursement.
- Flexible reimbursement policy for innovation treatment: In most of European countries, there is no special pricing and reimbursement regulation for orphan drugs. Orphan drugs are evaluated in the same approach as non-orphan drugs by evaluating cost-benefit ratio. However, justifying the ratio cost-benefit of a new orphan drug can be challenging because there is no reference treatment as a comparator and the number of participants in clinical trial can be very limited. Therefore, instead of using a cost benefit approach, many HTA bodies adopt a conditional reimbursement policy. The pharmaceutical companies can remain the same reimbursed price if they can assure the clinical performance in real life as proved in clinical trials. This approach permits pharmaceutical companies to retrieve their RD cost and assure their turnover, while proving the drug real life effectiveness and reducing the treatment to non-responding patients.

- Considering the social point of view about commercialization orphan drugs: Experience sharing by physicians and patients in clinical trials will provide more insight about the disease as well as effectiveness and security of orphan drugs. Moreover, the patient advocacy groups may help to diffuse information about new treatments available on markets, consequently, reduce the marketing costs. By applying the MCDA approach, patients and physicians 'view should be taken into account in pricing and reimbursement process. Social-economic factors collected from individual patients/patient advocacy groups will facilitate the elaboration of a successful healthcare coverage for different stakeholders[54].

### **Beneluxa**

Regarding the criteria of pricing and reimbursement, pharmaceutical companies and HTA may have different priorities. For pharmaceutical companies, a price is fixed based on research and development cost, number of potential patients and profit margin. Meanwhile, HTA may concern more about clinical performance, cost-effectiveness ratio, alternative treatments, innovative characters of the medicines. Negotiating price and reimbursement in each European country with national requirements may become a big challenge for the sponsor so that their new product can reach patients. In 2015, the first agreement for fixing pricing and reimbursement was signed by Belgium, Netherland and Luxemburg in order to set up the first common regulation about four areas:

- Common horizon scanning
- Common Health Technology Assessments
- Information exchange
- Common price negotiation.

This agreement proposes a triple benefit: secure national health budget, offer a larger market of orphan drugs for pharmaceutical company and accelerate the access to patients. This collaboration allows the health agencies to be aware of the price and reimbursement status in other countries. Thank to a larger potential patient, the HTA stand in a better position to negotiate

the price with the company. On the other hand, for the company, the procedure of price negotiation can be simplified. Moreover, their product is guaranteed to be commercialized in a larger population, which assures the turn over to cover the research and development cost. Finally, the patients may have access to the treatment faster than before[55].

## **France**

Price and reimbursement is decided at Haut Authority de Santé (HAS). Two perspectives of the new orphan drugs will be evaluated:

- Therapeutic value by Commission de Transparence (CT): This CT will elaborate two assessments: SMR (Service Médical Rendu – Therapeutic value) and ASMR (Amélioration du service medical rendu – Added therapeutic value).
- Medical-Economic value by CEEPS (Economic Evaluation Commission for Public Health). CEEPS will elaborate their opinion about economic impact on the national budget and this assessment will be sent to UNCAM (National Union of Assurance) for fixing the reimbursement level.

Evaluation of therapeutic value (SMR) is based on following criteria: severity of the disease, effectiveness and security of the treatment, position of the new treatment in current therapeutic strategy and benefit for public health. SMR allows to fix the reimbursement level of the new drug. There are four level of SMR: Important (65-100%), Moderate (30%), Weak(15%) and Insufficient (0%). Orphan drugs in France are reimbursed to 100% for innovate products and irreplaceable for life threatening diseases.

ASMR – added therapeutic assessment compare the new drug with existing treatment, if the new drug may offer a better security and tolerance for patients based on clinical data, medical need and impact on life quality for patients. There are six levels of ASMR from I as Major, and VI as non-recommended to be used in Public Health. For innovative medicines classified from ASMR 1 to 3 with a significant impact on national assurance budget, a medical economic assessment will be evaluated by CEEPS and sent to CEPS (Economic Comity for Health Products) together with ASRM classification to negotiate the price with the sponsor. For orphan drug application, there is usually no existing satisfactory treatment served as reference treatment and the market

size is limited. Therefore, pharmaceutical companies usually asked for ASMR class 1 with a high price to assure that the turnover can recover research and development cost.

However, these SMR and ASMR are re-evaluated every 5 years, so the price and reimbursement level can be changed if a new drug in the same indication is commercialized[56].

Among European countries, manufacturing price before tax and annual cost of orphan drugs is highest in France, following by Germany. It can be explained in the way that: in France, during Compassionate Use Program, price is fixed freely by pharmaceutical companies to fix and reimbursed 100%. When the price is fixed, the company is responsible to reimburse the difference. Moreover, France is one of the biggest pharmaceutical market in Europe. Hence, during the price negotiation, pharmaceutical companies try to maintain the same price as declared in Compassionate Use Program.

## **Germany**

Before 2011, drug prices in Germany were considered to be the highest in Europe, because the manufacturers were free to set the prices for new drugs. This led to increase the health expenditure in medical sector and the public expense on health did even exceed the GDP growth in Germany. Therefore, as of 2011, an Act to Reorganise the Pharmaceutical's Market in Statutory Health Insurance System (AMNOG) was introduced in Germany, in order to control the new patent drugs.

According to the AMNOG, manufacturers are still free to set their prices during the first year of marketing authorization. However, they are required to give the Statutory Health Insurance (SHIs) a discount of 7% on these products. AMNOG uses the early benefit of the company during these 12 months in order to reflect the additional benefit on the market, therefore, to determine the reimbursement rate.

One month after the Marketing Authorisation is granted, the sponsor is required to submit a dossier to the Federal Joint Committee (G-BA) to provide the additional therapeutic benefit of the new product, in compared to an appropriate comparator therapy fixed by G-BA. If there is no existing appropriate comparator therapy, a best therapeutic treatment can be negotiated with G-BA in advance. G-BA will provide a resolution and classify the new drugs based on the extent of

the additional benefit from (1)- major additional benefit to (6) as less benefit. At the same time, Institute For Quality and Efficiency in Health care (IQWiG- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) , an independent scientific institute, will evaluate and issue a cost-benefit report about the potential numbers of patients and the costs of the treatment. Only for orphan drugs, if the actual sales after the first year do not exceed 50 millions euros, the classification issued by G-BA will be maintained. However, if the actual sales exceed 50 million euros, a re-assessment will be conducted where both G-BA and IQWiG will be involved for re-evaluating the additional therapeutic benefits.

After the reimbursement classification is fixed, the price will be negotiated with the Central Federal Association of Statutory Health Insurance Funds (GKV-SV). This process can start 4 weeks after the publication of AMNOG and can last until 6 months. The decision on the price will be assessed based on the additional therapeutic benefit issued by AMNOG and the prices in other European countries. If the price negotiation cannot be achieved at the end of 6 months, arbitration will be initiated and will be regulated by an arbitration board ruling under German Social Code Book.

The negotiated price will come to effective as of 13<sup>th</sup> month after the market launch[57].

## **Italy**

In Italy, orphan drugs are evaluated by the same procedure as non-orphan drugs by law No 325. Prices are negotiated between pharmaceutical company and Pricing and Reimbursement Commission (CPR), who represents Italy Medicines Agency (AFIFA) and regional HTAs. The following criteria will be considered during evaluation process:

- Positive cost-effectiveness ratio
- Favourable benefit risk balance when compared to other drugs for the same indication
- Economic impact national health resources
- Daily cost per patient in compared to other treatment
- Estimation of acquired market shares

- Prices and reimbursement level in other European countries

In order to decide the reimbursement, the new orphan drug will be compared to other existing treatment, if it is dedicated to a disease with no existing treatment, or it may offer a better benefit risk balance of a better socio-economic benefit.

In Italy, orphan drugs usually obtain class A-H reimbursing for usage exclusively in hospital with 100% of reimbursement. In an inventory research of EURORDIS conducted for 60 orphan drugs in 10 European countries in 2010, it is showed that orphan drugs' prices in Italy are 150 -160% and 120-130% higher respectively to the lowest price and the mean value in 10 countries[26][58].

## **b2. Compassionate use of unlicensed medicinal products**

Beside the fast track or accelerate assessment of marketing authorisation, because of the severity and short life expectancy of patients diagnosed with rare diseases, an early access to treatment is possible in many European countries when the drug development is in the late phase of clinical trials and an application for marketing authorization via centralized procedure is expected. There are nearly 8000 rare diseases identified and patients affected by rare diseases are mostly children, who are unlikely to survive their 5<sup>th</sup> birthday. Participating in a clinical trial can be challenging and time consuming because of the strict criteria for enrolment. Therefore, compassionate use programs have become the light at the end of the tunnel for the patients and their families as well.

## **EMA**

The first legal basis for compassionate use was introduced in Article 83 of Regulation EC No 726/2004. Later on, in 2007, a guideline on compassionate use for human medicinal products (EMEA/27170/2006) issued by EMA came into force in order to give further guidance on conditions and procedures to be applied for concerned Member States[59].

It is stated in Article 83 of Regulation EC No. 726/2004 that a medicinal product can be the subject to a compassionate if three following conditions are fulfilled:

- The product is a treatment for a chronically severe or life threatening disease; where no efficient treatment is available

- The product is intended to be used in a group or a set of individual patients
- The clinical trials or a marketing authorization via a centralized procedure for this product is ongoing.

If a product is not eligible for a centralized marketing authorization or already obtains the Marketing Authorization, a demand of compassionate use is not possible. Under no circumstances that a compassionate use program can replace a well-defined clinical trial, however, the information about benefit/risk obtained during this program can be used to support the argument for obtaining Marketing Authorization. Physicians are encouraged to include their patients into a clinical trial before proposing a compassionate use program. An application for a compassionate program should be submitted to national Health Agency in concerned Member State. The concerned Member State would notify EMA and may request for CHMP'opinion about this compassionate use if needed.

All information about drugs that are allowed to a compassionate use program is published on EMA register, including: the name of product and concerned Member State, active substances/strength/ dosage/ indication, therapeutic population, CHMP opinion etc.

The evaluation procedure of compassionate use is in national level and depends on position of each concerned Member States. Since 2006, more than 50 requests of compassionate use programs have been submitted, 40% of those are for orphan drugs. 21 countries in Europe have adopted a legal framework to support the compassionate use except for Cyprus, Luxembourg, Ireland, Poland, Slovakia, Greece and Lithuania. Among the countries where compassionate use is possible, France, Germany, Italy, Spain and UK have the most structured legal framework to support compassionate use for patients. However, the access to an innovative orphan drug can be rapid in some countries like France, Germany and Sweden, but rather slow in other countries such as Belgium, Austria or UK[60][61].

## **France**

France is one of the first countries adopting the National Plan for Rare Diseases and has established numerous patient associations and centres to facilitate the research, diagnoses and medical treatments for both patients and health professionals (physicians, researchers etc)[26]. In

a survey conducted by EURODIS in 2011 on Compassionate Use Programs for 9 products in 42 European and non-European countries for a period from 2008 to 2011, France is the only country that was successful in conducting a CUP for all 9 products. From 2007 to 2010, it is estimated that France provided treatment to more than 20.000 patients (orphan or non-orphans) via Compassionate Use Programs[62].

In France, there are two possible approaches for using an orphan drug before obtaining the marketing authorisation: temporary use authorisation (ATU) or temporary use recommendation (RTU).

ATU is an exceptional use of a drug, which is already approved in another country but not France or still under development. An ATU is granted by French Health Authority (Agence Nationale de Sécurité du Médicament – ANSM), under strict conditions:

- The medicine is addressed to treat, prevent or diagnose the rare or life threatening diseases
- There is no alternative treatment on the market
- The applicant must provide scientific based information to prove the efficacy and safety of the medicine.

There are two types of ATU: nominative ATU and cohort ATU. A nominative ATU is used for only one assigned patient who is not taking any other biomedical research. The ratio benefice/risk must be proved by the applicant and the treatment must be request and strictly followed up by a specialized physician. A cohort ATU is granted for a group of patients when the ratio benefice/risk is strongly proved. The patients must be supervised strictly and the data must be collected as in Therapeutic Use Protocol. A nominative ATU can be requested only by a physician for an individual assigned patient, who cannot take part in a clinical trial. A cohort ATU can be requested by the marketing authorisation holder (MAH) who is engaged for a submission of marketing authorisation. Under no circumstance that an ATU can replace a clinical trial and the patient participated in a nominative ATU must not be part of a clinical trial before[63].

Another approach for an off label use in France is a temporary recommendation use (RTU). RTU

is applied for a product having obtained an AMM and under development for an orphan indication. A RTU can be granted by ANSM if the product can fulfil two following conditions[64]:

- The product is prescribed for an unmet medical need, where there is no existing or alternative treatment (marketed products or products under development).
- The ration benefice/risk must be proved to be favourable based on the current scientific data.

Thank to different legislation that allows an earlier access of orphan drugs to market, France is one of the countries where most of orphan drugs approved by EMA, including the rarest drugs, are available and 98% of patients diagnosed with rare diseases can have potential access to treatments[58].

## **Germany**

Compassionate use programs were first introduced in Germany in 14<sup>th</sup> Amendment of German Medicine Acts (GMA) and then updated in 15<sup>th</sup> GMA in 2009. It is stated in section 21, subsection 2 in 15<sup>th</sup> GMA that: following the Article 83 of Regulation EC No 726/2004, a medicinal product can be provided to patients with no marketing authorization if the disease is life threatening and there is no satisfactory treatment available[65].

In 2010, an Ordinance on medicinal products for compassionate use was issued by Federal Minister of Health in order to give more precise information about the definition of compassionate use, the information to provide for a notification, duration of program, obligations of the responsible person. The products distributed in compassionate use programs are free of charge and the information for all products under compassionate use programs is available in German on the website of BfaM. However, unlikely to France, there is no obligation that the compassionate use must be separated with clinical trials in Germany[26].

## **Italy**

There are two possibilities to prescribe an unauthorized product in Italy.

➤ **Fondo AIFA or Compassionate Use:**

Article 48, national legislation 326/2003 was elaborated to set a funding scheme for development of orphan drugs in Italy. According to this article, manufacturers or applicants are obliged to give part of their annual spending to national fund for orphan drugs and rare diseases by providing free of charge the unauthorized medicines to patients[26].

➤ **648 List**

The national legislation 648/96 allows patients to access to innovative products registered in Italian National Health System (SSN) where there is no alternative treatment available. It can be a product with ongoing clinical trials or off –label use for an authorized medicine. A product can be listed in 648 lists when there is no alternative treatment and one of the following conditions:

- No Marketing Authorization has been granted for this product in Italy. The medicine can be subject of an ongoing clinical trial or granted a Marketing Authorization in another country but not in Italy.
- For off label use: the indication has never been authorized in Italy before.

The request for 648 lists must be submitted by a physician and not a pharmaceutical company. Under no circumstances, a patient can benefit both 648 program and compassionate program at the same time. Once the Marketing Authorization is granted in Italy, the supply of this product either by Compassionate route or 648 route is stopped. (Italian Council of State Improves Access to Investigational Medicines) [66][26].

**c. Japan**

➤ **Price and Reimbursement negotiation**

If in the USA, orphan drug's price tends to be fixed freely by MAH and in Europe, the price fixation depends on each member state, Japan controls medicines' price by Central Social Insurance Medical Council (Chuikyo), a body of Ministry of Health Labour and Welfares. The reimbursement medicines will be listed in Drug Price Standard. MHLR published **Rule of pricing medicines** in the first time in 2016 and a revised version in 2018.

Drugs listed in Drug Price Standard can be prescribed in Insurance Medical Institution and reimbursed by National Health Insurance (NHI). Physicians and pharmacists working under national health insurance program are not allowed to prescribe the medicines outside of this list.

The price evaluation usually lasts between 60 and 90 days, as of the Marketing authorisation approval. Once the MAH obtain the approval, they can apply their product for NHI list. The proposed price is evaluated two times by Drug Pricing Organisation before Chuikyo gives final decision of approval or refuse. The NHI pricing list is revised 4 times per year for new drugs.

There are two phases in price fixation in Japan: price calculating and price adjustment.

### **Calculating phase:**

A new drug in Japan can be calculated in two ways:

If a reference drug can be used as comparator, the comparative method can be used. A comparable drug is chosen based on certain criteria: Indication, Pharmacological mechanism, Active ingredient, administration rout/ pharmaceutical form. The comparable drug must a brand name drug listed in NHI within the last 10 years without its generic listed during the same time.

Daily drug price matching will be calculated based on the current unit price of reference drug and number of pills taken per day by the formula below:

$$\text{Price of New drug} = (\text{unit price} \times \text{daily posology}) / \text{new drug's daily posology}.$$

When the new drug can prove its signification improvement compared to reference drug, a corrective percentage (premium) can be added. The added percentage is determined by added value of new drug. There are 5 categories of premium:

- Innovative Premium (70-120%): new action mechanism, outstanding efficacy/security, significant improvement of therapeutic scheme.
- Usefulness premium (5-60%): outstanding efficacy/security, significant improvement of therapeutic scheme
- Marketability premium (5,10-20%): Orphan drugs

- Child premium (5-20%): Paediatric indication
- Sakigake Designation (10-20%): it is for the innovative drug developed only in Japan.

If there is no comparable drug served as reference, which is usually the case for an orphan drug, cost calculation method can be utilized. The price is calculated based on:

- Manufacturing cost (raw material cost, personal expenses, production expenses)
- Sale and research cost
- Distribution cost
- Consumption cost.

### **Adjustment phase**

After the price is calculated by one of the aforementioned methods, it can be adjusted based on average foreign price calculated based on prices fixed in US, UK, France and Germany.

If the price calculated in Japan is 1.25 time higher than average foreign price, the price will be reduced:

$$\left( \frac{1}{3} \times \frac{\text{Temporally calculated price}}{\text{Average foreign price}} + \frac{5}{6} \right) \times \text{Average foreign price}$$

If the price calculated in Japan is 0.75 time lower than average foreign price, the price will be increased:

$$\left( \frac{1}{3} \times \frac{\text{Temporally calculated price}}{\text{Average foreign price}} + \frac{1}{2} \right) \times \text{Average foreign price}$$

Currently, drug's price in Japan is in the top 4 highest in the world, together with the USA and Germany and Canada[47]. Japanese way in price calculating reveals a weakness when the price negotiation phase has not yet terminated in other foreign countries. It was the case of Opivo novolumab, developed by Ono Pharmaceutical Co. As there was no foreign reference price, the price accepted in Japan was nearly 3 times higher than the price finally accepted in USA because it was granted 3 premiums (Biocentury, access and innovation in japan). As Japan encourages the

drug development firstly in Japan, MHLW is perfecting their system of price fixation and has implemented a trial of cost-effectiveness assessment since 2016 to re-evaluate the orphan drug's price[67].

### **Expanded Access Trial**

In Japan, the Notification No.0122-7 of Evaluation and Licensing Division came into force in January 2016 and allows using an unapproved drug with highly unmet medical needs outside the scope of clinical trials. The patients who are not eligible for clinical trials can be recruited into expanded access trials conducted from a compassionate point of view. This program can start at the earliest when the enrolment for clinical trials is completed and only for life threatening or serious debilitating diseases where there is no effective treatment available. The drugs distributed for this program must be quarantined from the other drugs in an appropriate way.

#### **➤ Patient-Requested Therapy System**

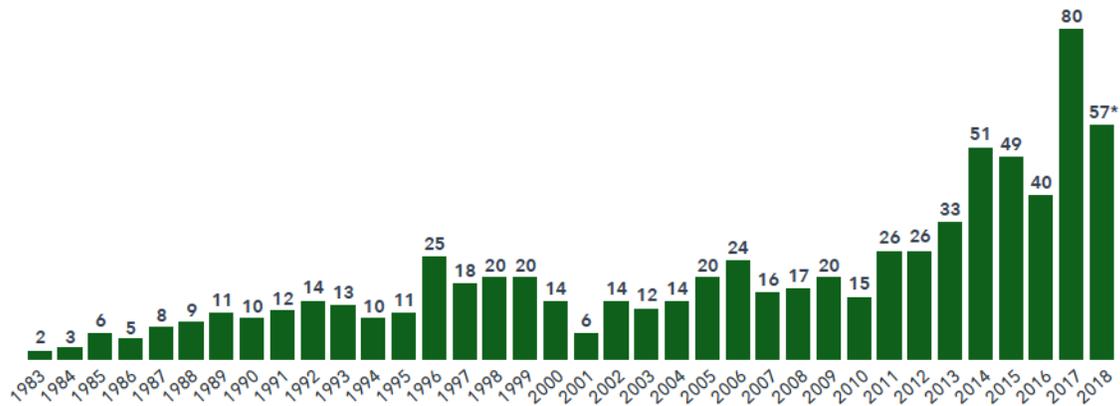
In April 2016, Patient-requested Therapy System came into effective in Japan, allowing a patient the possibility to submit a request to MHLW to receive an unapproved drug. In such case, the treatment is conducted as an uninsured concomitant therapy in a local medical institution, where the patient will be monitored. If the medicine has never been requested to be used as a patient requested therapy before, the clinical trial hospital centre will evaluate the request and send the application to MHLW with a protocol. If the medicine is requested previously, the clinical trial hospital centre will be able to judge the feasibility of the use. If the clinical trial is ongoing with the same indication requested by the patient, the patient should be considered to be included in the clinical trial or expanded access trial[68].

## **5. Orphan Drugs Registration Procedures**

### **a1. USA and Expedited Programs**

In the pharmaceutical world, the North American market is currently estimated to be the largest market in term of general sales (48,1% in 2017). In term of sales of new medicines containing new active substances firstly marketed in the world, 64.1% of new medicines are consumed in the United States[69].

The numbers of approval for orphan indications in the United States are illustrated in the graph below:



*Figure 8. Number of orphan indication approval in US from 1983 to 2018[26]*

The American Health and Medicines agency FDA (Food and Drug Administration) is considered as one of the leaders in drug's assessment and encouragement for pharmaceutical innovation. FDA is a complex agency consisted by different office and each office is divided into different specialized centers. Orphan drugs are assessed by Office of Medical Products and Tobacco. Most drugs, synthetic or biologics are evaluated by Center for Drug Evaluation and Research (CDER). However, some specific biological products are under the evaluation of Centre for Biologics Evaluation and Research (CBER), such as allergenic, blood and blood component, devices and tests used blood, blood components or cellular product, gene therapy, human tissues and cellular products, vaccines and xenotransplantation products[70].

### **Investigation New Drug Application**

The first step of drug registration in the United State is an Investigation New Drug application (IND) is required, which allows the medicinal product to used in clinical trials. The sponsor needs to provide information obtained in the pre-clinical phases regarding:

- Pharmacology and toxicology studies conducted in animal model: to ensure the reasonable security and efficacy of the drug once used in humans.
- Manufacturing information such as composition, manufacturer, stabilities and control tests during manufacturing process: to ensure that the sponsor is qualified to produce and

supply the product

- Clinical Protocols and Investigator Information: to assess the safety of clinical trials that there is no unnecessary risk and the trails are well controlled by qualified experts.

IND can be submitted to CDER or CBER, depending on the nature of the drug. 30 days after receiving a letter of acknowledgment, if there is no further notification, clinical trials can start, except for some emergency cases[70].

### **New Drug Application (NDA) or Therapeutic Biologics Application (BLA)**

When the results obtained from clinical trials are favourable, the sponsor can apply for a NDA to CDER or BLA to CBER if the product is classified as biologics. Since 2003, FDA has transferred the evaluation of some biologics from CBER to CDER such as: monoclonal antibodies for in vivo use, most proteins (except for vaccines and blood products), immunomodulators, grow factors, cytokines etc[72].

In 2014, Guidance for Industry-Expedited Programs for Serious Conditions-Drugs and biologics was issued by FDA in order to facilitate the development and evaluation for new drugs addressed to unmet medical need and treatment of serious/life-threatening conditions. The guidance provides four expedited evaluation process: Fast Track, Breakthrough therapy, Accelerated Approval and priority[73].

### **Fast track designation**

This procedure applies for drugs address for a serious condition and the sponsor can provide clinical/non clinical information to demonstrate the potential to unmet medical need. Evidence can be information obtained at early stage of development, such as non clinical studies or mechanism rationale. The sponsor will benefit from frequent meetings with FDA to support the development and can submit the NDA/BLA application in portions before a complete application.

### **Breakthrough therapy**

This designation applies for drugs addressed to serious conditions where other therapeutic treatments are available. If fast track designation accepts non-clinical data can support the

application, Breakthrough therapy designation requires preliminary clinical evidence that proves substantial improvement in some clinical endpoints in compared to existing therapies in at least one or two well-conducted multi-arm trials. For FDA, clinically significant endpoints are considered to have an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences. The sponsor should be able to provide sufficient justification why the chosen clinical endpoints can strongly predict potential effects of the investigational drug.

If granted A Breakthrough Therapy Designation, the sponsor will receive intensive guidance for development program since phase 1 of clinical trials by experts and senior managers from FDA. FDA may accept to review portions of a marketing application before the complete application is submitted (rolling review).

### **Accelerated approval**

Accelerated approval is usually used for long-term treatments that may need a long observation to measure clinical outcome. In order to be granted an accelerated approval, the treatment needs to fulfil the following criteria: it is addressed to a serious condition, can offer meaningful therapeutic advantage than other existing therapies or demonstrate an effect on an endpoint that can reasonably predict clinical benefit. Two types of endpoints that can be accepted is: surrogate endpoints such as a marker that can strongly predict clinical benefit or intermediate clinical endpoints that can be measured earlier than IMM.

For products approved by accelerated approval, there are conditions that a sponsor has to follow:

- During preapproval period: the sponsor must provide to FDA all promotional materials that are planned to distribute in 120 days after the approval.
- Post marketing authorisation trials are required to report the expected effects on IMM within a defined duration.
- The approval can be withdrawn if the post marketing authorisation cannot provide the expected clinical benefits in a fixed diligence or there is other information demonstrating the lack of safety/effectiveness of product in normal condition. If the sponsor provides

false or misleading information, the approval will be revoked at any moment.

### **Priority review**

Priority review applies for products addressed to serious conditions and can demonstrate the potential significant improvement in safety or effectiveness in not only treatment, prevention or diagnosis of a disease. The sponsor should provide justification for the superiority of their product in compared to available treatments on market.

For these four programs, FDA prefers that the sponsor should inform their intention to request for these designations as early as possible, ideally in pre-IND meeting. CDER or CBER may receive their request upon the nature of investigation drug. The evaluation for a fast track designation is 60 days and if approved, a designation letter is issued. For Accelerated Approval, there is no specific timelines for FDA response.

Products granted one of these expedited programs can benefit a Priority Evaluation from FDA. The evaluation is reduced to 8 months instead of 12 months for standard procedure. However, the details about evaluation process are not revealed by FDA.

### **a2. EU – Prime Program, Accelerated review and conditional MA**

The immerge of innovate treatment since several decades has become a challenging for both pharmaceutical companies and health agencies. In order to support the development and facilitate the evaluation process, PRIME was launch in March 2016 by EMA. The purpose of this program is to enhance the communication between sponsors and EMA in both scientific and regulatory terms during development of medicines that are potentially addressed to unmet medical need. Furthermore, the medicines in PRIME program will benefit an accelerated review by EMA. One specific rapporteur will be appointed by CHMP our CAT to support the medicine candidate. Regular meetings will be held in order to provide an overall development plan and advice for important phases. In order to benefit from PRIME program, a medicine candidate's target must be an unmet medical need where there is no satisfactory treatment or the medicine candidate can bring significant therapeutic outcome in compared to existing products or can improve the efficacy of existing treatments. According to EMA's overview, during two first year of PRIME program, most of products apply for PRIME are chemical, biological or advanced therapy

medicinal products (AMTPS) in oncology, Neurology and Haematology. 169 applications were submitted but only 36 were granted[73][75].

While applying for PRIME, the sponsor should be able to prove the candidate's potential to provide a significant benefit in an unmet medical need – proof of concept – based on preliminary clinical data. Most of applications sent to EMA were during phase 1-2 (43%) or phase 3 (72%). During two years, EMA denied 128 out of 169 requests, because of the following reasons:

- Products are too advanced in development to benefit from PRIME
- Lack of robustness in data
- Lack of sufficient efficacy
- Targets are not, or not yet, considered as unmet medical needs.

Among 36 products granted PRIME, 30 are orphan drug, 16 are for paediatric indication and 15 are ATMPs. 3 marketing authorisations are under evaluation in 2018[74].

The application should be submitted via Eudralink or to [prime@ema.europa.eu](mailto:prime@ema.europa.eu) according to timetables for submission and assessment published on EMA website. Usually there are 11 assessments per year[76]. If the submission is validated, a Scientific Advice Working Party (SAWP) and one EMA rapporteur will be appointed to evaluate the request. The report issued by SAWP will be evaluated by CHMP before final decision. The evaluation process may take up to 40 days since the validation. Once granted to PRIME program, the candidate will also be confirmed to benefit from accelerated review and appointed rapporteurs. The appointment for a responsible rapporteur may take one month. 6-7 months before MA submission, the sponsor needs to submit a letter of intent. CHMP co-rapporteur and PRAC rapporteur will be appointed accordingly[75].

Besides the scientific given by EMA, the Agency will also monitor the scientific results of drug development. PRIME program can be cancelled and withdrawn if the sponsor fails to provide the data regularly or there is new emerging evidence showing that the drug candidate is no longer eligible for PRIME support. However, this does not impact the centralized and accelerated procedure.

Since late 2016, EMA starts to exchange and compare the information with FDA regarding breakthrough therapy designation and PRIME. Sponsors that wish to have global launch may apply for Parallel Scientific Advice (PSA) program, where they will receive scientific advices and development support from both EMA and FDA[77].

### **Accelerated assessment – Procedure and timelines**

A standard centralised procedure can take up to 210 active days to obtain a final opinion from CHMP and 277 days to have EC decision. An accelerated assessment may last only 120 days to 150 days only.

#### **Pre-submission phase:**

6-7 months before submission, MAH should notify EMA about the request for an accelerated procedure. After this notification, a pre-submission meeting will be held between EMA and rapporteurs. 2-3 months before actual initial submission, an official submission of request for an accelerated procedure should be submitted to EMA[78].

30-day timetable for accelerated assessment is available on EMA's website[79].

#### **Evaluation phase:**

As of the D0 – official initial submission, assessment procedure is divided into 3 phases: 90-30-30 days. 90 days from the start of the procedure, CHMP will publish their first opinion, which can be positive or can lead to a list of question (LoQ). In case of questions, MAH has 1-month clock-stop to submit their responses in written or oral form. After the submission of responses from MAH, the clock is restarted at D91. It may take CHMP up to 30 days to issue their opinion. At D120, there is no stop of the clock. CHMP may address a List of Questions (LoQ) or List of Outstanding Issues (LoOI) and require MAH to provide written responses to their questions. The evaluation process continues at D121. After another 30-day evaluation, at D150, CHMP issues their final conclusion. Usually, LoQ and LoOI will be adopted on Tuesday to give MAH time to prepare for responses.

At D90 or D120, CHMP may require an explanation from MAH regarding the legibility of accelerated process. If MAH fails to provide a proof-based justification, the assessment process

can be switched to standard timetable[76][80].

### **a3. Japan**

After the USA, Japan is the second country in the world that developed a regulatory framework for development and registration of Orphan drugs. In 1993 was the first time, the term **orphan medicines/devices** was mentioned in Article 77-2 of Japanese Pharmaceutical Law (PAL). In Japan, the development of orphan drugs/devices is under the responsibility of three following bodies:

- Ministry of Health, Labour and Welfare (MHLW): responsible for evaluation of designation request and marketing authorisation, pre-designation consultation.
- Pharmaceutical and Medical Devices Agency (PDMA): responsible for scientific evaluation for clinical trials and marketing authorisation application.
- National Institute of Biomedical Innovation (NIBIO): responsible for guidance, consultation and financial support to MAH[35].

### **Japanese Breakthrough Therapy Designation – SAKIGAKE**

In parallel with Expedited programs in USA and PRIME in Europe, Japan has launched the SAKIGAKE program in 2016 to promote Research and Development for pharmaceutical innovation in Japan. Drugs granted for SAKIGAKE will benefit from PDMA consulting and guidance, a priority review for marketing authorisation (submission can be accepted in English, evaluation timeline is shortened to 3-6 months, submission of Phase III trial results can be done after New Drug Application Submission). However, in order to be granted SAKIGAKE designation, drug development (First in Human Study and Proof of Concept Study) must be conducted in Japan. This strategy is to encourage drug development by both Japanese companies and foreign companies, to make sure Japan is one of the first NDA in the world[81].

Although Japan is an ICH country, they have developed their own Pharmacopeia, Good Clinical Practice, Good Laboratory Practice and Good Manufacturing Practice. Registering a new drug in Japan can be challenging due to the different in culture, language as well as regulatory requirement. Japanese New Drug Application contains an application form, which is equivalent

to Module 1 of EU format, and Common Technical Document which includes Module 2-3-4-5 in EU format. The Application Form (Module 1) and Module 2 or GAIYO (Quality Overall Summary) must be in Japanese, meanwhile, Module 3-4-5 can be in English or Japanese[82].

Japanese Authority is extremely strict regarding quality and clinical data obtained in foreign countries.

While applying for marketing authorisation, if the MAH intends to import drugs to Japan from a foreign manufacturer, it is obligatory that this manufacturer is accredited by MHLW. PDMA will examine the local and facilities while MHLW will issue the Accreditation Certificate[83].

Regarding foreign clinical data, Japanese authority are highly concerned with drug-lag in efficacy and safety of new drugs, because of ethnic factors. In ICH E5 – Ethnic Factors in the acceptability of Foreign Clinical Data issued in 1998[84], the concept of **bridging data/studies for Efficacy and Safety** was firstly introduced to set the framework for extrapolating global clinical data (pharmacokinetic data, pharmacodynamics, dose response data etc) in a new region, taken into account the extrinsic and intrinsic ethnic factors. Bridging data packages are information obtained from Japanese patients, no matter their geographical location, therefore, the participants can be Japanese people living outside of Japan. Bridging studies are studies conducted on Japanese patients living in Japan only. The extrapolation is acceptable if the bridging studies show that the safety and efficacy of drug candidate are similar between original region and new region.

Further to the ICH-E5, PDMA published their own guideline in 2007 **Basic Principal on Global Clinical Trials**[85] to address their concern and their requirements for clinical data of drugs already approved by USA and EU. The guideline strongly encourages the foreign MAH to take into account the ethnic factors while conducting clinical trials and integrate healthy volunteer Japanese patients in Phase 1 of clinical trials to obtain dose-finding and safety data. Therefore, there are three scenarios for MAH:

- Full local development in Japan:
- Bridging studies

- Phase I conducted in both Japanese (living in or outside Japan) and non Japanese patients. If the studies show no ethnic sensitivity, extrapolation can be applied for phase II and Japanese patients can be integrated into phase 3- Global Clinical Trials. Japan can accept clinical data obtained from other Asian countries if Japanese patients are significantly present in the trial (15-20% of trial population).
- Global development: Multi-national trials

Bridging studies is a compromise solution for both foreign MAH and local Health Authority as it allows to reduce expense for local trials while avoid difference due to race and ethnicity among regions.

The guideline also indicates that, for orphan drugs development, when domestic dose finding studies or global clinical trials are difficult due to the rarity of patients/ diseases, PDMA may accept that Japanese patients are included only from a confirmatory Phase III trials, based on information obtained from other Asian/non-Japanese patients. In such case, the phase III trials should be conducted under a strict monitoring[85].

Similar to Scientific Advice from EMA, PMDA provides counseling for orphan drug application. In order to have counseling with PDMA, 8 weeks about the submission date, MAH should apply for a session. For non-orphan drug, this application can be done only on 1<sup>st</sup> working day of every month but for orphan drug, it can be applied on any working day. 5 days after receiving the application, PMDA announces the appointment schedule. 3 weeks later, MAH is supposed to submit the documents to be evaluated by PDMA. 4 weeks after the submission of documents, PDMA issues their opinion. MAH can also express their opinion to PDMA in case of disagreement. A face to face meeting can be arranged to clarify the questions. Expert team assigned by PDMA will give opinion and advice about development plan.

Orphan drugs can apply for a priority review by PDMA. The evaluation may take only 9 months instead of 12 months. The application is received by PDMA, who will issue a review report to MHLW. Before sending the report, PDMA may consult external experts if needed. MHLW may also consult their own experts in Pharmaceutical Affairs and Food Sanitation Council for scientific advice. MHLW will inform the application directly if the approval is granted. The

review process can be summarized the flow chart below:



Figure 9. Evaluation Process for New Drug Application by PDMA/MHLW [86]

A time limited conditional approval can be granted by MHLW for cellular and tissue based products. A conditional approval can be issued when safety and efficacy in a limited number of patients in a short duration clinical trial. This conditional approval is time limited and the MAH is due to provide confirmed information regarding efficacy and safety. Depending on the quality of provided information, the marketing authorisation can be revoked or fully approved[86].

## 6. Distribution and Dispensation

Once having marketing authorizations and price fixation, orphan drugs can be distributed directly by MAH or using an outsider companies. As orphan drugs usually have short development time and the treatments require a strict monitoring, they are mostly prescribed in hospital and reserved to some specialists only. The prescription right depends on each country policy. The dispensation to patients can be in special community pharmacies or specials health care units.

A research in availability of the last ten orphan drugs approved by EU in outpatient care was conducted in 2016 in 23 European countries. The results showed that in some countries such as: Austria, Germany, Norway, Malta, the drugs in research is dispensed in community pharmacies. Some other countries such as: UK, Slovakia, Poland, the medicines are mostly distributed in healthcare centers. Among these countries, patients in Malta were responsible for the whole payment of the treatment. In Austria, Germany, Norway, where medicines are available outside of hospital contexts, patients pay only partially the treatments or are distributed for free[87].

The distribution of orphan drugs is a strategy defined by each MAH. The limitation of distribution to a certain professional healthcare network allows the MAH to control better the

prices and the use of drugs after marketing authorization (patient follow-up, disease registries etc). In many cases, orphan drugs distributed in hospital pharmacies may have a lower price than those distributed in retail pharmacies because of difference in profit margins and the volume of potential patients. For example, in Italy, public price can be two times higher than hospital in order to limit the distribution outside of hospital pharmacies. Because of high prices, orphan drugs may be not arrive to patients in need[88].

In the USA, in order to increase the availability of orphan drugs to patients, treatments can be distributed to patients in both \*traditional\* channel -hospital pharmacies or \*non tradition\* channels – Specialty pharmacies. Specialty pharmacies are some limited exclusive pharmacies chosen by MAH to distribute the treatments and gathering patients' data. Because of high prices, not all retailed pharmacies are ready to invest hundreds of euros for drugs that will be distributed to very small patient population. Specialty pharmacies are usually well evaluated and equipped by a clinical expertise, management programs to optimize the treatments and report adverse events[48].

In USA, patients can access to rare disease treatment via patients support programs raised by pharmaceutical companies such as Sanofi or Pfizer. They provide patient education support via patient advocacy or individual case manager and also support in funding and insurance plan. Free or subsidized treatment can also be provided to patients under individual request if the medicines are not yet available in pharmacies due to price negotiation process[89][90].

In France, the national plan in 2005-2008 initiated the special hospital structure reserved for rare diseases (CRMR – Centre Référence Maladies Rares).[91] These are highly specialized reference centers about a group of rare diseases established in University Hospitals in order to offer a more efficient medical care to patients and to gain more knowledge about the rare diseases. The Competent centers are also established in regional levels around the Reference centers in order to facilitate the patient access. The list of Reference/Competent Centers and corresponding groups of diseases are revised every 5 years.[92] [93]

For the orphan drugs addressed to rare diseases with a reference/competent center, the initial prescription is reserved only to the physicians in the concerned centers. The prescriptions must comply exactly to therapeutic protocols. As orphan drugs are considered as innovative and costly

products, they are registered on a non-usual hospital list (Liste en sus – T2A). The hospitals distributing the products in T2A list will receive the full reimbursement by the National Health Insurance. In the latest T2A list, 7 orphan drugs are listed for 9 orphan indications: Naglazynme, Replagal, Soliris, Ucedane, Vimizim, VIPRIV, Spinraza. [94]

For orphan drugs with no Reference Centers, there is no obligation regarding the initial prescription. Depending on the initial prescription, the drug can be restrictively dispensed in a hospital pharmacy and administered to patients in hospital only. If the drugs are registered on retrocession list, with an authorisation issued by hospital pharmacy, the drugs can be dispensed at community pharmacy and administered at home.

The prescription renewal depends on the initial prescription. In case of prescription renewal, the initial prescription must be proved that the treatment was prescribed in a reference center. In case the patient is hospitalized in a medical unit belonging to the same reference center, the prescription itself is sufficient to prove the authenticity. Otherwise, the prescriber for renewal needs to complete a liaison form, which will be validated by initial prescriber in the reference center before the any dispensation for renewal. [95][96]



Figure 10. Orphan Drug Circulation in Hospitals in France

## **PART IV. CHALLENGES, OPPORTUNITIES AND GROWING TRENDS IN ORPHAN DRUG DEVELOPMENT**

### **A. Challenges in developing treatments for rare diseases**

#### **1. Early Drug Discovery**

During the last decades, thanks to incentives from health authorities, there has been an increasing need in research and development treatments for rare diseases, which requires a profound understanding the nature of rare diseases. Better understanding in pathology will allow to have better diagnostic and better drug discovery strategy. However, low prevalence of patients and lack of understanding about the disease leads delay in disease's recognition and limitations in evaluation of treatment efficacy and patient recruitment for clinical trials.

Patients with rare diseases are not easy to identified and usually misdiagnosed due to a poor awareness of healthcare professionals in this domain or insufficient healthcare system, which leads to poor information in epidemiology. Patients may have to try different healthcare institutions for long time before being able to find appropriate specialists. After reaching appropriate healthcare professionals, it may take numerous visits before they specialists may come to an accurate diagnostic. Many healthcare professionals, nurses and specialists admits that they have never heard of (some) rare diseases before. The lack of clinical symptoms usually leads to wrong diagnosis. The diagnosis of a rare disease can be a hurdle for patient's family and impact their life quality in many aspects, especially financially. The patients may have to overcome numerous inefficient biology tests, which may not be covered by insurance plan. Furthermore, patients may reach out for medical help only when clinical symptoms are clear. Delay in diagnosis and associating burden may make many patients and their family to quit before they can reach an appropriate specialist for an accurate diagnosis. As 80% of patients suffering rare diseases are children, who do not pass their fifth birthday, many patients many not survive before they receive an accurate diagnosis[97].

Among nearly 8000 rare diseases currently identified, 80% have genetic origins; however, there is no confirmed relation between genetic defect and pathological phenotype. Many rare diseases can be inherited but may also result from sporadic mutations or due to external exposures. For example, Gaucher disease was first discovered in 1930s but it took nearly 40 years until 1970s that the etiology of the disease can be explained. Gaucher disease can be divided into 3 subgroups, that affect both male and female, with different clinical manifestations (brain damages or not) and patient's life expectancy may vary from two to fifty years[98]. In contrary, many rare diseases may share several clinical signs at the beginning but were proved to have different genetic disorders. Leukemia is not a single disease but a group of diseases that share the same biological sign of high white blood cells. Different types of leukemia may have different mechanism, which leads to different therapeutic strategies. Many rare diseases may have unrelated initial clinical symptoms but turn out to have the same genetic disorders. Identifying the similarity or differences in causal genetic disorder allows better characterization of the disease and motivates a better orientation in research and development. Heterogeneity in genetic defects and clinical manifestation cause a great limitation in characterize a rare disease[99].

## **2. Clinical trials**

Clinical trials are imperative for any new drug development. Increased need for rare disease treatments leads to an increase in conducting clinical trials in this area. However, clinical trials on rare disease can be extremely challenging in compare to non-rare diseases.

In clinical trial design, the randomized controlled trial, which is often considered as a standard for clinical trial, usually require hundreds of participants, longtime duration and a comparator arm. All of these factors may be impossible for rare diseases because of absent standardized treatment small patient population with geographically dispersion and low life expectancy. Many patients, after many misdiagnosis, may not survive until the end of trials[100].

Recruiting patients for rare disease clinical trials is hurdled for most sponsors because of patient dispersion and children involvement. Because of rarity and geographically dispersion of patients, sponsors may have to search for patients in different countries and conduct multi-national trials in worldwide in order to find patients that suitable for trial's criteria and ensure statistical validation in results. Recruiting patients worldwide require an access to patients' registry in various

countries to determine if patients are eligible of the trials, identifying competent investigational centers then persuading patients to participate. It may become competitive if there are several sponsors conducting research for the same disease. Furthermore, 80% of patients suffering rare diseases are children, it is scientifically and ethically hurdler for sponsors to engage patients and parents. Most children with rare disease have extremely short lifespan, and many fatal diseases can rapidly progress, understandably parents would want their children to receive active treatment care and are not ready to enroll their children in trails where placebo can be administered. For many diseases that have significant physical impairment, traveling to clinical centers may be unbearable hurdle for patients and their family to remain in clinical trials. In addition, due to limited knowledge about disease and nature history (disease development, unexpected life threatening adverse events etc), healthcare professionals participating in clinical trials may need to have specific training programs. A close collaboration between sponsors, patient advocacy, clinical centers and various supporting for both patients and physicians may require, hence clinical trials for rare disease can be extremely costly for sponsors[100].

Evaluating clinical trial outcome can be especially difficult for sponsors because the challenge in choosing validated measurement tool in rare disease. The lack of understanding in disease pathogenesis and nature history, heterogeneous genetic etiologies and clinical presentations may lead to unappropriated endpoints. Genetic and biological markers can be useful to assess treatment's response for a small group of patients with similarity in genetic causality. Nevertheless, due to geographically dispersion and ethnically diversity, choosing patients with specific genetic patterns may prolong the recruitment. In addition, as most rare diseases affect children at young age, it is difficult to obtain self-assessment in effect of treatments. This usually base on parents help and physician's evaluation. Many diseases can progress rapidly, patients and their family can no longer be able to provide a consistent comparison of treatment's effect[99][101].

### **3. Regulatory barriers**

Despite the effort for early access (compassionate use) and accelerated review process, many orphan drugs, after obtaining Marketing Authorization are never actually on the market because of difficulties in price and reimbursement negotiation with each national healthcare. In a study

conducted by EURODIS in 2010 on 60 orphan drugs in 10 European countries, 22 % of orphan drugs was claimed as **unknown** by national authorities. It is estimated treatments are unavailable for nearly 30% of approved orphan drugs in this study. The highest availability for orphan drugs are in metabolic diseases (64%) and rare cancers (59%). Countries where orphan drugs are the most available are Netherlands, France and Denmark. Meanwhile, in Spain, Greece and Romania, only around 33% approved orphan drugs are available to patients[56].

Currently, there is no harmonized legislation about health-technology assessment. Each country has their own criteria about benefit/risk and socio-economic balance in negotiating the price and reimbursement level with sponsors. Due to the challenges in research and development phase (low prevalence, clinical trials conducted in limited duration and nonstandard conditions, lack of robust information in safety and efficacy etc.), national Health Technology Assessment bodies usually evaluate the value of new orphan drugs in lack of information and find it challenging to elaborate a comprehensive evaluation. It is difficult to estimate the added value, the benefit/risk ratio and the therapeutic place of new treatment. Moreover, the target patient population in each country can be very small and their life span can be short, it is difficult to estimate the cost-effectiveness ration of new treatment in real life[99].

Price fixed by sponsors are usually high because it is calculated based on research and development cost, manufacturing cost, market size, cost and utility ratios[102]. It is estimated that, annual cost per patient receiving orphan drugs can vary between 1,200 euros to 400,000 euros with a median cost being 32,000 euros [103]. Furthermore, price and reimbursement level also depend on socio-economic standard and affordability in each country. As a result, abovementioned factors tend to discourage national HTA bodies to elaborate a positive reimbursement level. Many orphan drugs if being assessed as a classic medicine, may never be reimbursed, as a result, may never reach patients because of high prices[99].

## **B. Opportunities and Trends in Development Orphan Drugs**

### **1. Highly profitable for pharmaceutical companies**

Despite a small patient population, orphan drugs are becoming highly profitable in pharmaceutical markets. Worldwide orphan drug sales are estimated at 138 billions dollars in 2018 and may achieve 262 billion dollars in 2024. For the period of 2013-2017, mean non-orphan drug per patient per year are only 30,708 dollars meanwhile, mean cost per patient per year for orphan drug is estimated at 147,308 dollars, approximately 5 times higher. Soliri, the highest revenue per patient in USA (500,000 dollars//patient/per year), is currently treating less than 2500 patients in 2017. There may be a substantial financial benefit for big pharmaceutical companies, who are willing to invest into ultra-rare diseases[104]. It is believed that orphans drugs can potentially generate equal revenue to non-orphan drugs with only less than 20% of share of prescription[105].

Increased knowledge in gene sequencing and gene therapies in the last several decades enable to shorten early discovery and development time. Once the proof of concept is confirmed, development time from phase 2 to launching time for orphan drugs can be faster than traditional medicines (3,9 years vs 5,42 years). Clinical trial's size for orphan drugs is usually smaller and there is higher potential for regulatory process (93% vs 88%). In additional, pharmaceutical companies receive financial incentives from government, which help to reduce development and research's expense[105].

### **2. Incentives from Health Authorities**

The products granted Orphan Drug Designation receive incentives offered by Health Authorities before and after the Marketing Authorization. The incentives may vary among FDA, EMA or PDMA, but usually focus on four domains: scientific assistance during development phase, accelerated/priority review for marketing authorization application, marketing exclusivity and financial incentives.

Once the product is granted Orphan Drug Designation, sponsors will receive scientific advice under Protocol Assistance or Consultation at reduce fee or free charge from EMA/FDA/PDMA at

any stage of drug's development. Health authorities will provide advice to sponsors for a better demonstration of quality, benefit/risk report and safety. This exchange with Health Authorities at early development phase helps to reduce the risk of refusal at marketing authorization evaluation. FDA, EMA and PDMA encourage the parallel scientific advice in order to facilitate the evaluation and increase the possibility of marketing the same product in their countries[106].

Designated Orphan Drugs are titled for an accelerated or priority review with reduced fees and the shorter expected timeline of evaluation (6 or 9 months). In Europe, Designated Orphan Drugs are assessed under Centralized Procedure, where only one application is needed and the marketing authorization is valid in all European Member States[106].

All three Health Authorities provide market exclusivity to designated orphan drugs: 10 years in Europe and Japan, 7 years in the USA once the drug is approved. After Orphan Drug Designation, if a pediatric development plan is submitted, an extra 2 years of market exclusivity will be added[107].

The Market Exclusivity is application for each orphan indication. After marketing authorization, this patent enables the drug to be protected from competition with other application of Marketing Authorization or Line Extension of similar medicines with similar indications. Two products can be granted Orphan Drug Designation for the same indication, but marketing exclusivity will only apply to the first who obtains the approval of Marketing Authorization. Another Marketing application can be reviewed for the same indication if it is considered as \*not similar\* to the existing patent drug. In such case, the second Marketing Authorization application needs to prove a significant benefit in quality, effectiveness and safety in compared to the currently approved drug and will be considered case by case[106].

Regarding financial incentives, FDA and Japan provide Orphan Drug Grant Programs such as Orphan Drugs Clinical Trials Grants, Subsidy payment, *Drug Fund for Side-Effects Relief and Research Promotion* etc in order to cover research and development fees. EMA does not offer research grants for orphan drugs developers but Findings for Research and Development projects in rare diseases are available. Beside reduced fees for regulatory assessment, sponsors are also granted for tax reduction: such as 12 % tax reduction in Research and Development in Japan, 50% of tax credit for clinical trials conducted in the USA[107][108].

There is no tax reduction granted by EMA but each Member State may provide their own support (exemption of certain tax categories, total reimbursement for products in compassionate use etc)[109]

In additional, there are further financial incentives for Small and Medium Size enterprises who develops orphan drugs: exemption or % reduction of charges for Protocol Assistance, pre and post authorization inspection, application fees, annual fees for the first year[110][111].

### **3. Advantages of Compassionate use**

From a market access point of view, designated orphan drugs usually benefit an earlier and wider access to patients thanks to compassion use programs even if the drug has not yet obtained Marketing Authorisation in the country.. Because of unmet medical need and long price negotiation, Health Authorities may accept to reimburse the treatment to 100% at prices estimated by sponsors, therefore it allows the sponsors to have revenue on products even when it has not yet officially launched. On the other hand, in some cases, many sponsors would prefer to provide treatments for free before price and reimbursement is fixed in key countries. In term of global health, compassionate use for free open access to patients in poor countries, where health authorities cannot afford for the payment. In some developing countries, compassionate use is the only way patients can access to treatment via humanitarian programs. It is estimated in 2015 that nearly 100% of treatment for Gaucher patients in Bosnia, Jordan and Macedonia is provided via humanitarian basis. For sponsor's strategy, providing orphan drugs via compassionate use may establish network with healthcare professionals in the country hence; facilitate their place on the market. In addition, compassionate use program is usually strictly monitored with a transparent system of undesirable effects registry, which allows sponsors to collect data about drug's effectiveness in real life condition[60].

### **4. Repurposed Drugs**

Development cost can be reduced more significantly if orphan drugs are developed from an established/approved medicinal product (repurposed drugs). In such case, sponsors may not be required to conduct a full development program from non-clinical to clinical phase. Development time for a repurposed drug can reduce to 3-12 years in compared to 10-17 years for a new drug.

(a) TRADITIONAL APPROACHES TO DRUG DEVELOPMENT	TARGET DISCOVERY	DISCOVERY & SCREENING	LEAD OPTIMIZATION	ADMET	DEVELOPMENT	REGISTRATION	MARKET
	2 – 3 years	0.5 – 1 years	1 – 3 years	1 – 2 years	5 – 6 years	1 – 2 years	
10–17 year process Small probability of success	Expression analysis; <i>In vitro</i> function; <i>In vivo</i> validation; Bioinformatics.	<b>DISCOVERY</b> Traditional Combinatorial chemistry Structure-based drug design <b>SCREENING</b> <i>In vitro</i> <i>Ex vivo</i> and <i>in vivo</i> HTS/HCS.	Traditional medicinal chemistry ; Rational drug design.	Bioavailability and systemic exposure (absorption, clearance and distribution).	Must start clinical testing at Phase I.	United States (FDA) Europe (EMA) Japan (MHLW) Brazil (ANVISA) Rest of world.	
(b) DRUG REPOSITIONING	COMPOUND ACQUISITION	COMPOUND ACQUISITION	DEVELOPMENT	REGISTRATION	MARKET		
	1 – 2 years	0 – 2 years	1 – 6 years	1 – 2 years	MARKET		
3–12 year process Reduced safety and pharmacokinetic uncertainty	Targeted searches Novel insights Specialized screening platforms Serendipity.	Licensing Novel IP Both licensing and novel IP Internal sources.	May start at preclinical, Phase I or Phase II stages; Ability to leverage existing data packages.	United States (FDA) Europe (EMA) Japan (MHLW) Brazil (ANVISA) Rest of world.			

Figure 11. Traditional new drug vs Repurposed Drug Development timeline[107]

As being developed from active ingredients already approved and marketed, the characterisation of active molecules are well known. Information regarding pharmacology, pharmacokinetics, toxicology and clinical safety information are already available from previous marketing authorisation application. Hence, preclinical and phase I clinical trials can be exempted. Bridging studies or bibliographical researches may be accepted by health authorities. In some cases, additional preclinical/clinical trials for new formulation and safety in new usage may be necessary. As a result, there is less risk of failure in drug's development as well as in regulatory process[112].

Repurposed drugs and novel drugs have to go through the same evaluation process. However, repurposed drugs appear to obtain approval more frequently than novel drugs (30% vs 11%). Repurposed drugs can still obtain patent protection for new usage if sponsors can prove that this use is innovative than existing treatment. However, it is shown in reality that, repurposed drugs may have longer time in price and reimbursement negotiation than novel drugs. In a study in 112 orphan drugs approved in 2017, the average time from EMA approval to launching in local is at least 11.7 months (France) and can prolong to 15.4 months in Italy [113].

Lower cost of research and development leads to low price after marketing authorisation and permits orphan drugs become more affordable for patients and insurance payers. Repurposing drugs make orphan drugs' development possible for not-for-profit organisations to be MAH sponsors. According to a study conducted by EuOrphan in 2017, besides 93% of MAH as industries, 6% of orphan designation belongs to individuals, hospital/university and charity/non-profit groups. However, none of these are MAH holders yet[114]. The future of affordable or low cost orphan drugs is in repurposed drugs.

Sector	Orphan designation	MA sponsor
Individuals	31 (2.8%)	0
Hospital/university	26 (2.3%)	0
Charity/patient group/not-for-profit	19 (1.7%)	0
Industry	1034 (93.1%)	93 (100%)
Total	1110	93

*Figure 12. Number of Orphan Designation Application in each sector of Sponsor [109]*

Regarding regulatory barriers for repurposed drugs, in USA, regulatory framework has been developed for repurposing drugs since 1999 by FDA and CDER. Drugs candidates fir repurposing must be submitted to Section 505 (b)2 regardless for orphan or non-orphan indication. It has been shown that in USA, approvals for NDA are granted twice for repurposed drugs than novel drugs. Applications by Section 505(b)(2) are possible when at least one of studies that the application relies on was not conducted by the applicant.. FDA accepts published literature that applicant has not obtained the right of reference or Agency's finding of safety or effectiveness for approved drugs. If the applicant can claim the right of reference for the data, the application will fall under a full NDA - 505(b)(1)[115][116].

In Europe, similar regulatory pathway was established by Article 10 of Directive 2001/83/EC, issued by EMA in 2001. However, there is several significant difference in compared to Section 505(b)(2) [106]. EMA authorizes the use of non-proprietary studies in application only if applicant conducts studies tailored to the differences from reference listed drugs. Moreover, Article 10 is not applicable for a new molecular entity. Only changes from reference listed drugs are accepted for application under Article 10. In reality, due to Intellectual Property of original drugs, most

of repurposed drugs are approved in a new marketing authorisation application because of different usage, mode of action to initial indication. Otherwise, a new drug without reformulation will benefit only original MAH/ manufacturers. If initial drugs are registered under MRP/DCP/NP procedures, new orphan indication will require a new marketing authorisation application to EMA. If initial drugs are in CP procedure for non-orphan indications, it is not possible to group a non-orphan and orphan indication under the same authorisation. A new marketing authorisation for orphan indication will be required or a withdrawal for existing indication is needed[117].

In practice, it is more advantageous for MAH to apply for a new orphan designation and marketing authorisation in order to benefit from patient protection, market exclusivity and financial incentives from EMA. While starting a drug repurposing project, applicants should consider the market exclusivity of previously approved drugs with same indication. On the other hand, for an old drug whose patent is expired, a repurposing project with orphan indication can give the new drug 7-10 years of market exclusivity, plus 2 years in case of paediatric incentives[118].

## PART V. CONCLUSION

Since the first legislation for orphan drugs came into force in 1983, Thanks to these efforts from government, healthcare actors and patient advocacy, rare diseases and orphan drugs have captured the attention of pharmaceutical industry. More than 500 orphan drugs have been approved in the USA and over 120 treatments for rare diseases are available in Europe. Health Authorities have elaborated regulatory framework, provided scientific and financial support for national and international development plan. Despite the fact that the knowledge about rare diseases has been considerably increased over the last 36 years, the amount of treatable rare diseases remains insignificant among more than 8000 identified rare diseases. Orphan drug development faces challenges in most of drug development phases, from understanding the nature of diseases and orienting in early drug discovery, conducting clinical trials to obtaining marketing authorization and market access. Targeted patient population for orphan drugs are mostly children with short life expectancy. It is extremely challenging to obtain parents' consent for clinical trials and to measure effectiveness of medicinal products as the treatment and follow up depend on their family and parents. In some other cases, patients desire to receive treatments but may be opposed by their parents for different reasons (benefit/risk ratio, religious reasons etc). From a regulatory point of view, major Health Authorities (FDA, EMA, and PDMA) have succeeded in harmonizing to certain extent the requirements on orphan drugs under development. Unfortunately, handling an approved orphan drug in post Marketing Authorization phase depends on national policy in each country. Unfortunately, only a small proportion of approved orphan drugs can actually be given to patients due to the complexity in fixing national price and reimbursement categories. Ethically speaking, different countries and cultures may have different point of view regarding the balance between \*equity\* vs \*equality\*, global health vs rare severe diseases. International harmonized guidance in health-technology assessment is expected to be developed in order to facilitate the access to patients in future.

On the other hand, rare diseases and orphan drugs are unmet medical needs therefor, it have become tendency in research and development in the recent decades. With a small but highly profitable patient population and various incentives given by health authorizes, not only big pharma but small and medium sized companies have succeeded in development and marketing orphan drugs, which makes orphan drugs \*less rare\* to patients. As most of rare diseases have

genetic origins, with today advanced gene and cellular technology, understanding the nature of diseases and developing therapeutic strategies have become more feasible and less time-consuming than 40 years ago. Rare diseases and orphan drugs are not only a profitable market for ICH countries but also non ICH countries. Many Asian countries with high living standard and efficient health system such as Taiwan, Hong Kong, Singapore have developed legal basis in order to facilitate the entry of orphan drugs in their countries[119]. In developing countries in South East Asia, Africa, South America, rare diseases have been sensitized via different public health campaigns and treatments are available via humanitarian programs[120]. In conclusion, despite various challenges, orphan drugs development is a confirmed potential niche in both scientific and industrial perspectives.

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## SERMENT DE GALIEN

*Je jure, en présence de mes maîtres de la Faculté, des conseillers de l'Ordre des pharmaciens et de mes condisciples :*

- ❖ D'honorer ceux qui m'ont instruit dans les préceptes de mon art et de leur témoigner ma reconnaissance en restant fidèle à leur enseignement.*
- ❖ D'exercer, dans l'intérêt de la santé publique, ma profession avec conscience et de respecter non seulement la législation en vigueur, mais aussi les règles de l'honneur, de la probité et du désintéressement.*
- ❖ De ne jamais oublier ma responsabilité et mes devoirs envers le malade et sa dignité humaine, de respecter le secret professionnel.*
- ❖ En aucun cas, je ne consentirai à utiliser mes connaissances et mon état pour corrompre les mœurs et favoriser des actes criminels.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre, méprisé de mes confrères, si j'y manque.*