

# Challenges in the Research and Development of Orphan Drugs: A Review

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## ABSTRACT

Pharmaceutical agents which treat rare medical conditions like orphan or rare diseases are called "orphan drugs". The name 'orphan' itself indicates that the pharmaceutical industries are showing less interest in the development and marketing of drugs intended only for a small number of patients. Difficulty in the diagnosis and therapeutic management of rare disease is the major challenge in the development of orphan drug.

In recent years, progress has been made in the development of orphan drugs by pharma industries due to enactment of different regulations, administration authorities, tax benefits, marketing rights and public awareness by different countries. This review provides an overview of incentives, marketing rights and administrative authorities of different countries like U.S, European Union, South Korea, Japan, Australia and Taiwan.

*Keywords: Rare diseases; incentives; tax benefits; marketing rights; public awareness.*

## 1. INTRODUCTION

Rare diseases are often rare and referred to as "orphan diseases." They are even life threatening, mostly affecting neonates, infants and children below 5 years of age. The term "orphan disease" suits for rare disease in several ways mainly

1. Neonates, infants and children are mostly at more risk in most of the rare diseases.
2. Orphan disease means lack of control [1].

According to WHO, the prevalence of rare diseases is 0.65%-1%. Eighty percent of rare diseases are detected as genetic origin, in which 50% of rare diseases affect children and 30% of patients die before the age of 5 years with rare diseases. The definition of rare diseases slightly differs by region.

WHO defines.

Rare disease is often debilitating lifelong disease or disorder with a prevalence of 1 or less per 1000 population.

### 1.1 US Defines [2,3],

Condition or disease that affects fewer than 2,00,000 patients.

### 1.2 Japan Defines [4-6]

A disease of unknown etiology with no effective treatment that presents a major financial and psychological burden and that is rare (fewer than 50,000 total patients).

### 1.3 South Korea Defines

Diseases that affect fewer than 20,000 people or diseases for which an appropriate treatment or medicine has yet to be developed.

### 1.4 Taiwan Defines

A disease that is prevalent in fewer than 1 in 10,000 population, has a genetic origin and is difficult to diagnose and treat.

### 1.5 China Defines

A disease that is prevalent in fewer than 1 in 5,00,000 or has a neonatal morbidity of fewer than 1 in 10,000 [7].

### 1.6 Australia Defines [8]

A disease is considered rare if affects 1 in 2,000 people.

## 2. CHALLENGES IN RESEARCH AND DEVELOPMENT OF ORPHAN DRUGS [4,9,10]

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There is no universal definition in case of rare diseases. These are severe, chronic illnesses that can limit life expectancy. As of 2019, there are nearly 6,000 to 8,000 rare diseases. Some rare diseases affect few people, while others affect a huge population, such as sickle cell anemia which affects huge people of Africa, Middle Eastern, Asian origin but rare in other countries.

A disease may be rare in one region but common in other regions. Example: Pompe disease which is more common in Africa, America and some parts of Asia but rare in other countries.

Pharma industries showing negligible interest in the development of drugs and treatments for rare disease as the process of drug development is a costly process [8]. Rare diseases provide little financial incentive for the pharma sector to develop and market medicinal products for diagnosis and prevention [11,12]. Other complications for the development of drugs for rare diseases are

1. unknown / less understood pathophysiology

2. Unavailability of approved preclinical models
3. Unavailability of standard comparator drug
4. Unknown natural history of disease
5. Shortage of diagnostic criteria.

### **3. INCENTIVES FOR ORPHAN DRUG DEVELOPMENT IN DIFFERENT COUNTRIES [10,13-22]**

In most of the countries, orphan drug development research is dependent on government incentives. Many countries and regions have a special regulatory authority, such as Office of Orphan Products Development (OOPD) within the US Food and Drug Administration (FDA), European medical agency (EMA) in Europe, Ministry of Health, Labour and Welfare (MHLW) in Japan, Department of Health (DOH) in Taiwan, SFDA in China and Korean Food and Drug Administration (KFDA) in South Korea.

Fast track approvals, fee waiver, market exclusivity are some of the benefits offered by the governments to encourage research in

**Table 1. Correlation of the regulation of rare diseases and orphan drugs between different countries [4, 16]**

<b>Category</b>	<b>USA</b>	<b>Australia</b>	<b>Japan</b>	<b>UE</b>	<b>Taiwan</b>	<b>South Korea</b>
Regulation	Orphan drug act (1983)	Orphan drug policy (1998)	Orphan drug regulation (1993)	Regulation (CE) (2000)	Rare disease control and orphan(2000)	Orphan drug guideline(2003)
Administration authority	Office of orphan products and development (OOPD)	TGA (Therapeutic good administration)	OPSR/MHLW (Ministry of Health, Labour, Welfare)	EMA/COMP (Committee for Orphan Medicinal Products)	DOH (Department of Health)	KFDA (Korean Food and Drug Administration)
Tax benefits	50% for clinical studies	NO	6% for any type of studies + limited to 10% of company's corporation tax	Managed by member states	-	-
Marketing rights	7 years	5 years	10 years	10 years	10 years+ 2 years	6 years
Public awareness	National Organisation for Rare Disorders (NORD)	Rare disease patient organisations	Intractable Disease Information Centre- established in 1997 <a href="http://www.nanbyou.or.jp">http://www.nanbyou.or.jp</a>	European organisation for Rare Disease (EURORDIS)	The Taiwan Foundation for Rare Disorders(TFRD) <a href="http://www.tfrd.org.tw">http://www.tfrd.org.tw</a>	The Korean Rare Disease Information Database <a href="http://helpline.cdc.go.kr">http://helpline.cdc.go.kr</a>

orphan drugs. In India, CDSCO issued a notice regarding waiver of fees for the clinical trials for approval of new drugs in the Indian population, for drugs which are already approved in outside India. The waiver of fees is especially on orphan drugs for rare disease and drugs indicated for diseases and conditions with no therapy.

#### 4. CHALLENGES IN THE DIAGNOSIS OF RARE DISEASES

Most of the rare diseases, nearly 80% are of genetic origin and usually affect children. Lack of proper diagnostic methods making rare diseases more complicated for invention of treatment or therapies. Now-a-days detection of rare diseases became much more rapid with the invention of 'Next Generation Sequencing(NGS)' technology. Precise diagnostic results can be obtained within 4-8 weeks with Next Generation Sequencing which took years earlier. Rare disease genes can be detected at a much earlier stage by using specific NGS techniques like Whole Exome Sequencing, Clinical Exome and Whole Genome Sequencing (WGS).

##### 4.1 Types of Genetic Test [23,24]

There are different types of genetic tests available for diagnosis of rare diseases. They are

1. Trio Exome Analysis
2. Whole Exome Analysis
3. Clinical Exome
4. Targeted Gene Panel

##### 4.1.1 Trio exome analysis

It helps to identify variants which are De novo as well as which have been inherited from parents. It is usually a collaborative analysis of affected and unaffected members (commonly parents and patients).

##### 4.1.2 Whole exome analysis

It is a complete test that looks at all the exome sequences that are present in the human genome.

##### 4.1.3 Clinical exome

It screens all the genes in a human body which are responsible for human disease.

##### 4.1.4 Targeted gene panel

Targeted Gene Panel consists of a selected set of gene regions or genes that are responsible for association with certain diseases.

**Table 2. List of FDA approved orphan drugs [26,27]**

Name of rare disease	Brand name	Manufacturer
Acquired Haemophilia A	ELOCTATE	Bioverativ
Arginino succinic aciduria	Ravicti	Horizon pharma
Barrett oesophagus	Photofrin	Pinnacle Biologics
Cerebral palsy	Dysport	Ipsen Limited
Dravet syndrome	Diacomit	Biocodex
Ewing sarcoma	Votrient	GSK
Follicular lymphoma	Aliqopa	Bayer
Glioma	Gleolan	NX Development corporation
Homocystinuria	Cystadone	Orphan Europe SARL
Infantile apnea	Cafcit	Bedford Laboratories
Japanese encephalitis	Ixiaro	Intercell AG
Keratoconus	Photrexa viscous	Avedro, Inc
Laron syndrome	Increlex	Tercica , Inc
Mucormycosis	Cresemba	Astellas
Oslam syndrome	Fusilev	Spectrum pharmaceuticals
Paget disease of bone	Cibacalcin	Novartis
ROHHAD	Gonal-f	EMD Serono, Inc
Sezary syndrome	Poteligo	Kyowa kirin
Turner syndrome	Humatrope	Eli Lilly

**Table 3. Current clinical trials and studies in the field of rare diseases/orphan drugs [26,27]**

<b>Disease</b>	<b>Drug</b>	<b>company</b>
15q duplication syndrome	TAK-935	Ovid Therapeutics
Acromegaly	lonis -GHR-LRx	lonis pharmaceuticals
Canavan disease	BBP-812	Aspa Therapeutics
Danon disease	RP-A501	Rocket pharmaceuticals
Hunter syndrome	Elaprase	Shire
Krabbe disease	PBKR03	Passage Bio
Lupus nephropathy	Ravulizumab	Alexion pharmaceuticals
Myasthenia gravis	ARGX-113	Argenx
Prurigo nodularis	vixarelimab	Kiniksa pharmaceuticals
Rett syndrome	Trofinetide	ACADIA pharmaceuticals
Still's disease	Anakinra	Swedish orphan Biovitrum
WHIM syndrome	Mavorixafor	X4 pharmaceuticals

## 5. TREATMENT [24,25]

Genome analysis is used to diagnose different diseases. Now-a-days gene transfer therapies are successful in patients. For replacing missing genes viral vectors are used effectively in gene therapy. A disease causing protein can be modified or blocked using Gene disruption technologies like antisense oligonucleotide, RNA interference (RNAi), microRNA modulation. Cancer can be treated by changing chimeric antigen receptor (CAR) Tcells by using Gene modified cell therapy. Clustered regularly interspaced short palindromic repeats (CRISPR) and zinc finger (ZFN) technologies are used to directly modify in-vivo and ex-vivo genes by employing Gene editing. Drug approvals for rare diseases are increasing persistently in this decade. List of FDA approved orphan drugs and drugs in clinical trials are mentioned in Tables 2,3.

## 6. CONCLUSION

In the present scenario, there is no doubt that due to implementation of various regulations, tax benefits, and marketing rights there is a drastic lift in the availability of medicines for rare diseases. Now -a -days major multinational companies are funding in the field of rare diseases. Though there has been a prominent development in the field of orphan drugs for various rare diseases, still there is no medication and therapies available for many rare diseases which show the importance of implementing the right strategies for understanding the risks and benefits in the development of orphan drugs.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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