A STUDY OF REGULATORY ASPECTS ON REGISTRATION OF ORPHAN DRUGS IN U.S & E.U

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ABSTRACT

The medicinal products used in the treatment, prevention, and diagnosis of rare disease like Myoclonus disease, Huntington's disease, Tourette syndrome are called as Orphan drugs. When it comes to defining rare disease and approving them as “Orphan designations.” The Criteria varies from country to country based on severity, prevalence of the disease and alternative therapies available.

In 1983, the US government brought the Orphan Drug Act to facilitate and encourage pharmaceutical company to develop orphan drugs without which they showreduced interest in the research and development of these drugs. The reason being their low market value and sales of orphan drugs is so miniscule that it will not enable them to even recover a fraction of the investment made in them.

After the inception of “Orphan Drugs” act 4500 orphan designations have been approved, 730 biologic drug products have been approved to treat 250 Orphan designations.

In the past decades, orphan designations have doubled in number when compared to its preceding decade but only 1/5th of the developed medications to treat them and received regulatory approval.

Key Words: Orphan drugs, rare disease, orphan designations, world health organization, food and drug administration, European medicinal agency.

1.INTRODUCTION

Drugs are pharmaceuticals used for the evaluation diagnosis or medication of rare often fatal or severely disabling diseases.

The name orphan comes from the Greek word “orphanos," meaning a baby does not have parental care. Rare diseases are sometimes referred to as orphan diseases because no drugmanufacturing

company was prepared to adopted them. As a result, rare diseases resemble orphan infants who have no parents and have historically necessitated drug development efforts. [1]

A Rare or Orphan condition affects a smaller amount of the people and its causes could or could not be determined by genetics.[2]

As defined by the World Health Organization, rare diseases are diseases or conditions that have a prevalence of less than 1 in 1000 of the population. The NIH classified diseasesto be rare disease or condition when they prevalencein 200,000 people or less in the US. There are primarily two differences between the two definitions. First, in Europe, rare diseases are more commonly defined as diseases or conditions that affect no more than 5 in 10,000 people. Second, according to DSM, the orphan drug designation is made in the United States.[3]

However, in order to provide the best equipment to their people physicians vary their recommendations based on the sort of illness a few of their definitions depend only on the number of individuals coping with a hardship and other considers like the existence of appropriate treatments or the severity of the situation. [4]

Some of the orphan drugs along with the disease treated:

- **OPDIVO:**Bladder Cancer, Colorectal Cancer, Melanoma, Non-Small Cell Lung Cancer (NSCLC), and Liver Cancer have all been approved by the FDA.
- **RITUXAN:** Rituxan is exceptional in that it is authorised for the treatment of autoimmune and cancer conditions such as rheumatoid arthritis, non-Hodgkin's lymph, and chronic lymphocytic leukaemia (CLL).
- **REVLIMID:** Currently, the FDA has given Revlimid's approval for the treatment of newly diagnosed cases of myelodysplastic syndromes (MDS), multiple myeloma,and patients with multiple myeloma who have undergone autologous hematopoietic stem cell transplantation.

1.1 ORPHAN DRUG ACT

An orphan drug act that was instituted in the USA in 1983 was world’s first law to designate drugs for development purposes Canada, Australia, Europe, Japan, and Singapore. All have similar laws in place Canada and Russia are in the process of formulating their laws the drug act in the USA set up new advantages for sponsors.

Which is intended to improve the options for treatments for rare disorders this classification only means that the sponsor is eligible for specific advantages during the process of drug development.

Within the United States of America, The OOPDin the FDA grants orphan Designation to any product used for the rare diseases described above. Orphan status can be granted at any time during the drug

development procedure. A product designated as an orphan drug can later receive market approval only when clinical study data demonstrate the product's safety and efficacy.

Orphan status confers certain benefits to sponsors; a 50% tax credit on clinical development costs, application fee waivers, grants to conduct clinical trials, and 7 years of market exclusivity.

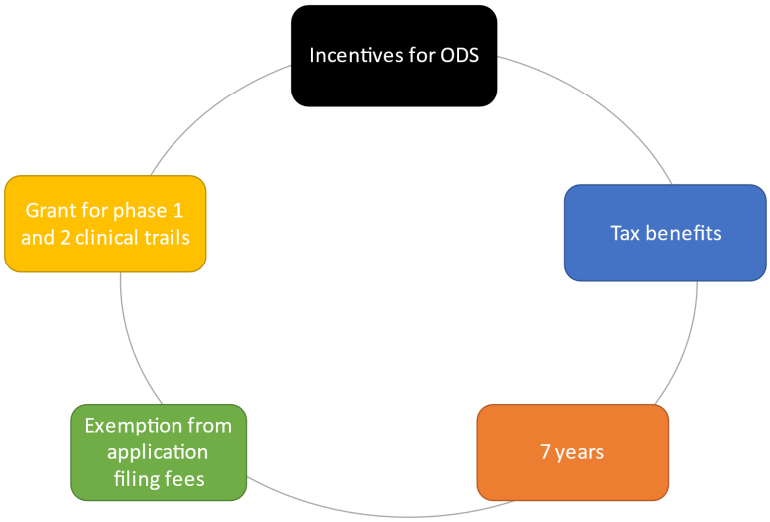

Figure-1.1: ShowingOrphan status confers certain benefits to sponsors

Those Incentives sincerely have a huge effect on orphan drug improvement within the decade earlier than the orphan drug act only 10 merchandises for uncommon illnesses received advertising authorization and more than 10 products have been approved for marketing each year since then, and about 430 products have been approved for rare diseases to date. OOPD additionally administers an associated application designed to inspire the improvement of scientific devices for the treatment or diagnosis of uncommon sicknesses. [5]

1.2 REGULATIONS OF ORPHAN DRUG IN US

Definition

In US, a drug or biological product can diagnose as an orphan drug if its far used to prevent treat or diagnose a situation that affects fewer than 200000 patients.

Criteria for orphan designation status in the United States

For a drug to receive orphan drug status, the following criteria must be met:

- ✓ A drug that has not been accept before.
- ✓ A drug with a new orphan indication.

✓ A drug is shown to be clinically superior to a previously approved drug.[6]

1.2.1ORPHAN DRUG REVIEW PROCESS IN US

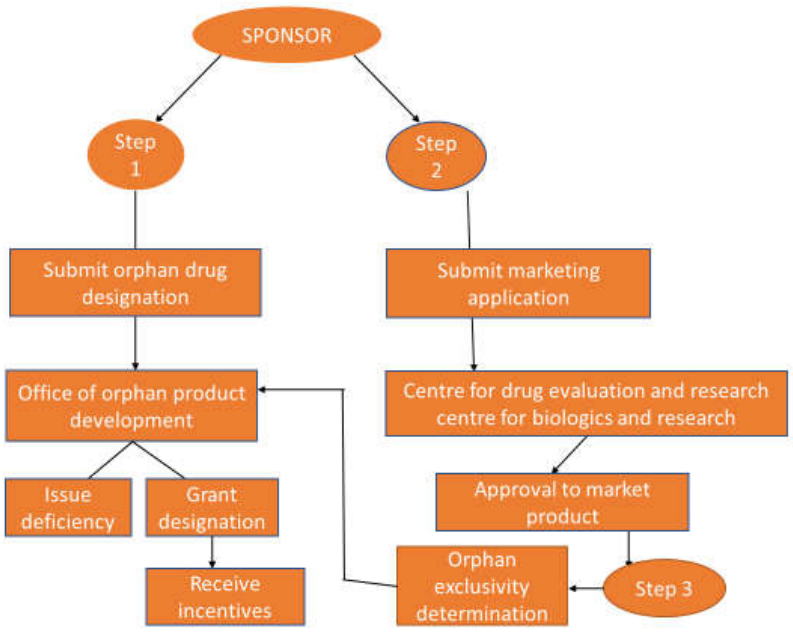

Figure-1.2.1: ShowingOrphan drug review process in US.

1.2.2INCENTIVES

- **Protocol Assistance:** Giving scientific advice to the developers of designated orphan medicines for rare diseases.
- **Waived Regulatory Fees:** Giving some exemptions,reduces fees while filing NDA for orphan drugs under PDUFA.
- **Tax Credit:** Gives a credit of 50% of the clinical testing costs for the development of drugs.
- **Clinical development benefits:** The Orphan products were granted funding for clinical trials to advance rare disease research and the development of orphan drugs.
- **Seven Years Marketing Exclusivity**:7-year market exclusivity is decided by using the office of Orphan Product development (OOPD) upon advertising and marketing approval of the drug.[7]

S. no.	Basic elements	Description
1	Administrative information	Descriptive name of the product Manufacturer for drug substance/drug product.
2	Explaining what is the disease or condition	Mechanism of action of drug pathophysiology, Etiology, Treatment options, Prognosis
3	Providing sufficient scientific rationale	Drug description and MOA relevant to disease/condition. in vitro, in vivo, clinical studies data relevant to drug and disease/condition
4	Determining the population estimate to support that the disease is rare.	Foreign, geographically restricted, or old data Registries, databases, literature searches Estimate must be current as of the time of application submission All calculations and references used to derive the population estimate

Table 1: Documents Included in the Orphan Designation Application in US

USFDA APPROVED ORPHAN DRUGS -FY 2022

S.no	Generic name	Trade name	Orphan designation	Market approval date
1	Stiripentol	Diacomit	Treatment of Dravet syndrome.	07-14-2022
2	Carfilzomib	Kytrolis	Treatment of multiple myeloma.	06-30-2022
3	Crizotinib	Xalkori	Treatment of inflammatory my fibroblastictumour.	07-14-2022
4	Lisocabtagenemeraleucel	Breyanzi	Treatment of follicular lymphoma	06-24-2022
5	Sodium phenyl butyrate	Pheburane	Treatment of urea cycle disorder	06-17-2022
6	Setmelanotide	Imcivree	Treatment of Bardet- Biedl syndrome	06-16-2022
7	Vutrisiran	Amvuttra	Treatment of transthyretin mediated amyloidosis	06-13-2022
8	Risdiplam	Evrysdi	Treatment of spinal muscular atrophy	05-27-2022
9	Tisagenlecleucel	Kymriah	Treatment of follicular lymphoma	05-27-2022
10	Nivolumab	Opdivo	Treatment of esophageal cancer	05-27-2022
11	Ivosidenib	Tibsovo	Treatment of acute myeloid leukemia.	05-25-2022

12	Treprostinil	Tyvaso dpi	Treatment of pulmonary arterial hypertension	05-23-2022
13	Dupilumab	Dupixent	Treatment of eosinophilic esophagitis	05-20-2022
14	Azecitidine	Vidaza	Treatment of juvenile myelomonocytic leukemia.	05-20-2022
15	Tecovirimat	Tpoxx	Treatment of small pox	05-18-2022
16	Edaravone	Radicavaors	Treatment of amyotrophic lateral sclerosis.	05-12-2022
17	Mavacamten	Camzyos	Treatment of symptomatic hypertrophic cardiomyopathy	04-28-2022
18	Ravulizumab - cwvzs	Ultomiris	Treatment of myasthenia gravis	04-27-2022
19	Alpelisib	Vijoice	Treatment of pik3ca – related overgrowth spectrum.	04-05-2022
20	Axicabtageneciloleucel	Yescarta	Treatment of follicular lymphoma.	04-01-2022
21	Fen flouramine	Fintepla	Treatment of Lennox – gas taut syndrome.	03-25-2022
22	Sirolimus	Hyftor	Treatment of angiofibroma associated with tuberous sclerosis.	03-22-2022
23	Ciltacabtageneautoleucel	Carvykti	Treatment of multiple myeloma.	02-28-2022
24	Sutimlimab- jome	Enjaymo	Treatment of auto immune haemolytic anemia.	02-04-2022
25	Emtricitabine and tenofovir alafenamide	Descovy	Treatment of HIV -1 infection in pediatric patients under 12 years of age	01-07-2022

Table 2:Showing USFDA Approved orphan drugs in 2022

USFDA APPROVED ORPHAN DRUGS – FY 2021

S.no	**Generic Name**	**Trade Name**	**Orphan Designation**	**Marketing Approval Date**
1	Voxelotor	Oxbryta	Treatment of sickle cell disease	12/17/2021
2	Efgartigimod alfa-fcab	Vyvgart	Treatment of myasthenia gravis	12/17/2021
3	Carfilzomib	Kyprolis	Treatment of multiple myeloma	11/30/2021

4	Vosoritide	Voxzogo	Treatment of achondroplasia	11/19/2021
5	Asciminib	Scemblix	Treatment of chronic myelogenous leukemia	10/29/2021
6	Coagulation factor IX	Benefix	Treatment of hemophilia B	10-05-2021
7	Maralixibat	Livmarli	Treatment of Alagille syndrome	09/29/2021
8	Ruxolitinib	Jakafi	Treatment of graft versus host disease	09/22/2021
9	Zanubrutinib	Brukinsa	Treatment of splenic marginal zone lymphoma	09/14/2021
10	Ivosidenib	Tibsovo	Treatment of cholangiocarcinoma	08/25/2021
11	Belzutifan	Welireg	Treatment of von Hippel-Lindau disease	08/13/2021
12	Selexipag	Uptravi	Treatment of pulmonary arterial hypertension	07/29/2021
13	Immune globulin intravenous	Octagam 10%	Treatment of dermatomyositis	07/15/2021
14	Cyclosporine	Verkazia	Treatment of vernal keratoconjunctivitis	06/23/2021
15	Posaconazole	Noxafil	Treatment of invasive aspergillosis	06/17/2021
16	Infigratinib	Truseltiq	Treatment of cholangiocarcinoma	05/28/2021
17	Nivolumab	Opdivo	Treatment of esophageal cancer	05/20/2021
18	Nivolumab	Opdivo	Treatment of esophageal cancer	04/16/2021
19	Crotalidae Immune F(ab')2 (Equine)	Anavip	Treatment of envenomation by Crotaline snakes	04-01-2021
20	Isatuximab-irfc	Sarclisa	Treatment of multiple myeloma	03/31/2021
21	Idecabtagenevicleucel	Abecma	Treatment of multiple myeloma	03/26/2021
22	Casimersen	Amondys 45	Treatment of Duchenne muscular dystrophy	02/25/2021
23	Umbralisib	Ukoniq	Treatment of splenic marginal zone lymphoma	02-05-2021
24	Carglumic acid	Carbaglu	Treatment of organic acidemias	01/22/2021
25	Crizotinib	Xalkori	Treatment of anaplastic large cell lymphoma	01/14/2021

Table 3:Showing USFDA Approved orphan drugs in 2021. [8]

1.3CASE STUDY

Withdrawal of Orphan drug designation request for Remdesivir by Gilead:

- US FDA eliminated orphan medicinal product as an ability covid-19 remedy later complaint that medication covid-19 is a unique disorder changed into “disingenuous”.
- Gilead Pharmaceuticals requested from the FDA that the classification be removed, allowing the company a longer absolute lifespan instead of 7 to 5 years and significant tax incentives immediately after it was granted.
- Remdesivir is going to allow virus duplication is a medicine presently being inspected as an ability remedy for covid-19 via numerous clinical tests.
- Orphan acceptance be a structure plan to encourage the improvement of medication for uncommon condition in which there can be a most effective a small wide variety of human beings fewer than 200 000 humans inside the us that might be treat.
- Ameet Sar Patwari, a senior lecturer of medicine at Harvard College and the senior supervisor of this device on rule restoration and regulation, stated that the orphan drug act was supposed to enable the improvement of medicines for which there was no real prospect of manufacturing a profit. which is challenging to understand in the case of a treatment for an active pandemic.
- Tahir Amin declared; Gilead made the right choice in withdrawing theOrphan drug designation status. But it was not supposed to happen in the first place. Because COVID-19 is widespread and will also coexist with other species in our ecosystem, Companies are developing vaccines for ensuringthe human beings will be protected. When a vaccine is available, everyone will probably want or need to acquire it.
- If accepted, Gilead’s remdesivir also may probably end up as a primaryline remedy for upcoming flu seasons, so to claim that this is an unprecedented sickness would be to neglect whatever the future holds like if its complete show increases some of the Gilead’s motivation and the FDA’s decision,which makes it appear as though it has been captured.
- Despite the orphan medication status being dropped, Amin said, Gilead will continue to receive a 5-year exclusivity period for novel molecular entities in addition to the present patent exclusivities that last until at least 2038.
- Given that now the patent will still be in effect it raises the concern of what the FDA will do with it in the event of a pandemic. [9]

2.ORPHAN DRUG REGULATIONS IN THE EUROPEAN UNION

Definition: the disorder is taken into consideration to be uncommon if it happens in fewer than five in 10,000 human beings.

The EU gives numerous incentives to inspire organizations inside the studies and development of drugs for uncommon diseases that in any other case would not be developed. corporations can follow for orphan designation for medicine to access these incentives which meet sure standards proposed by using the EMA.

Although the prevalence of rare diseases is especially low, nearly 27 to 36 million people (or 6% to 8%) of the EU population are affected. Most rare diseases impact children, and nearly 30 percent of them dies before the age of 5. Given these facts, research into the origins and mechanisms of rare diseases and therefore the field of orphan drug development has become increasingly important for the EU Commission and public health organizations.

Criteria for orphan designation status:

- Lesser than 5 out of 10000 populate in the EU may have the complication.
- Medicines must treat prevent or diagnose life-threatening or chronically in capitating conditions if not unlikely that the drug exists doubtful to generate enough revenue to excuse the evolution funding.
- Where no appropriate diagnostic prophylactic or therapeutic methods exist or where drugs already exist that would provide significant additional benefit to the affected population.

2.1 REVIEW PROCESS OF ORPHAN DRUGS IN EUROPE

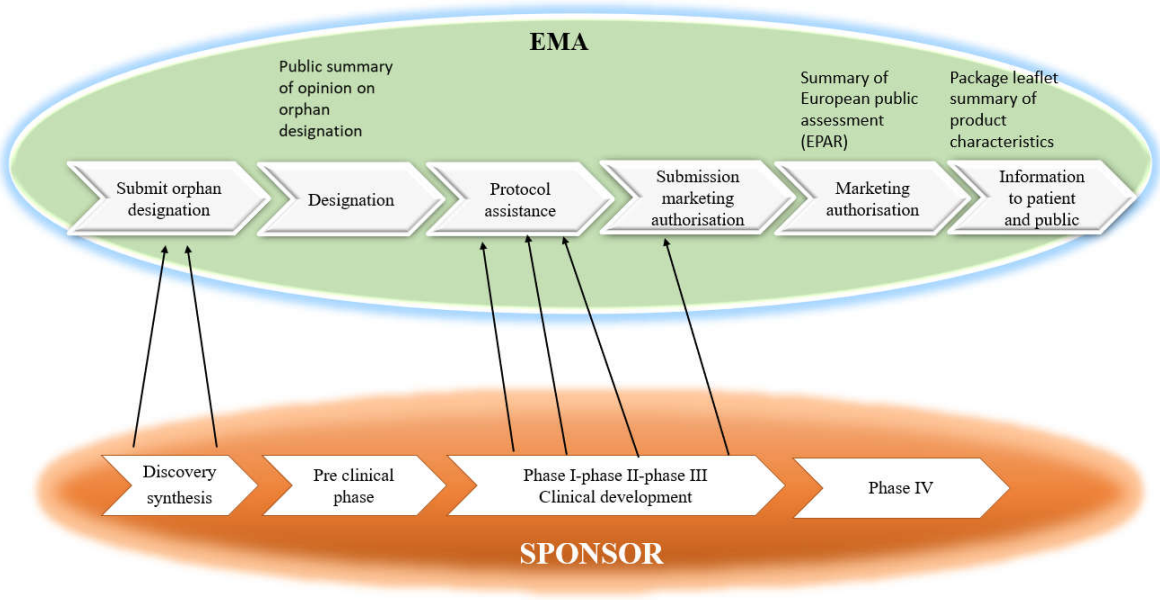

Figure 2.1: ShowingReview process of orphan drugs in Europe. [10]

2.1.1 INCENTIVES

- **Protocol assistance:**A type of medical recommendation unique for distinctive orphan medicines. This permits sponsors to get solutions to their questions about the forms of studies needed to show the medication pleasant benefits and risks and statistics at the vast advantage of the medicine.
- **10 years of Market exclusivity**. This era of safety is prolonged by means of 2 years for drug treatments that also have complied with an agreed pediatric research plan granted at the time of overview of the orphan medicinal drug designation
- **Fee reductions:** Organizations applying for specified orphan drug treatments pay decreased costs for regulatory activities. This includes decreased expenses for protocol assistance, advertising-authorization programs, inspections earlier than authorization packages for modifications to marketing authorizations made after approval and reduced annual expenses
- **Grants:**The organization does no longer provide studies offers for sponsors of orphan drug treatment, but the EU commission and different sources can also provide funding.
- **Centralized authorization procedure:**All orphan specific medicines are assessed for marketing authorization centrally within the European Union.[11]

2.2 Applying for orphan designation

Applications for medicinal product orphan drug designations should be submitted to EMA in accordance with the procedural guidelines on the structure and substance of orphan drug designation programmes.

From 19 September 2018, candidates want to publish packages for orphan designation and pre- and post-designation activities the usage of EMA's novel comfortable on-line machine IRIS.

The orphan drug designation utility incorporates a briefing report (sections A to E) describing the involved medicinal product, the proposed orphan indication and clinical statistics assisting the orphan drug designation application.

As outlined in Article three of EC law No. 141/2000 an orphan drug designation utility can both be primarily based on the low prevalence and prevalence rate within the European or where an enough return of funding without incentives is questionable.

In both cases, enough information has to be provided which must be presented inside the application following particular regulations as outlined in Article 2 of EC law No 847/2000 and following supportive procedural guidance files provided by way of EMA.

List of documents included in the orphan designation applicationin EU

Sr. no.	List of documents	Description	Format
1	Application form	Administrative information. Sponsor information - Corresponding contact person - OD number	Web form in EMA‟s online system IRIS.
2	Scientific document: Section A to E	Information on the medicinal product - Proposed orphan drug indication. -Medical information. - Justification of the life-threatening or chronically debilitating nature of the disease. - Data on the prevalence of the condition or disease. - Potential return of investment.	Word/RTF format
3	Proof of establishment of the sponsor in the EU	The sponsor must have a permanent physical address in the European Community.	PDF
4	Translations	Name of the product and the proposed orphan indication translated into all official languages of the European Union, incl. Icelandic and Norwegian	Word
5	References	Scientific articles cited throughout the application as single PDF files	PDF

Table 4: Showing Documents included in orphan designation application.[12]

2.3 Number of orphan medicinal products with European Union Designation in Europe

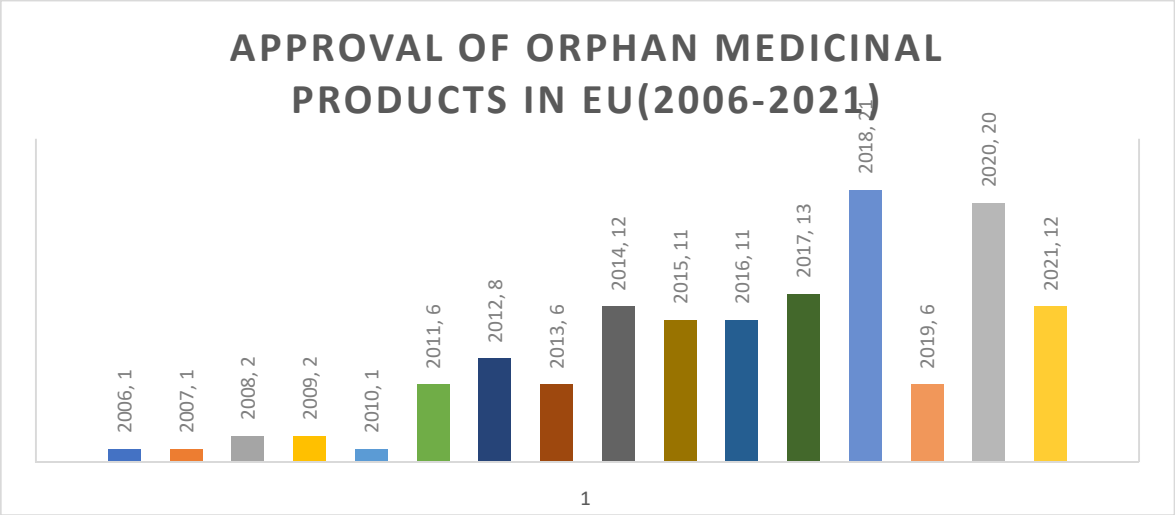

Figure 2.3: Showing Orphan Medicinal Products Approved in EU.

<u>Orphan medicinal products withdrawn for E.U</u>

S.NO	Tradename	Active substance	Market Authorization Date	Orphan Designation Withdrawal Date
1	CARBAGLU	Carglumic acid	28-01-2003	28-01-2013
2	GLIVEC	Imatinib mesylate	18/09/2006	16/04/2012
3	INOVELON	Rufinamide	16-01-2007	18-01-2019
4	JAKAVI	Ruxolitinib	28-08-2012	20-02-2015
5	NEXAVAR	Sorafenib tosylate	19-07-2006	22-07-2016
6	REVLIMID	Lenalidomide	14-06-2007	19-06-2017
7	SOLIRIS	Eculizumab	20-06-2007	22-06-2019
8	TORISEL	Temsirolimus	19-11-2007	21-11-2017
9	TRACLEER	Bosentan monohydrate	17-05-2002	17-05-2012
10	VIDAZA	Azacitidine	17-12-2008	22-12-2018
11	YONDELIS	Trabectedin	28-10-2009	31-10-2019

Table 5: Showing Orphan Medicinal Products Withdrawal from EU.[13]

Orphan designation withdrawal assessment report:

S.NO	Active substance	Orphan Indication	Application submission date	With drawl date	Condition
1	(S)-N-(5-((R)-2-(2,5-difluorophenyl) pyrrolidin-1-yl) pyrazolo[1,5-a] pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate	Treatment of soft tissue sarcoma	24-Aug-18	11-Jul-19	Intention to Diagnose, Prevent or Treat- Positive. Chronically debilitating and/or life-threatening nature-a 5-year relative survival for soft tissue sarcoma of 58%. The COMP noted that soft tissue sarcoma with an overall 5-year survival rate of approximately 60%. Number of people affected or at risk-r has been estimated to be 1 per 10,000.
2	Larotrectinib	Treatment of salivary gland cancer	24-Aug-18	11-Jul-19	Intention to diagnose, prevent or treat- Positive. Chronically debilitating and/or life-threatening nature-with 5-year survival for stage IV disease of 35-40%. The COMP noted that the that salivary gland cancer d 5-year survival rates ranging from 30% to 40%. Number of people affected or at risk - has been estimated to be 0.196 per 10,000.

3	Larotrectinib	Treatment of glioma	24-Aug-18	11-Jul-19	Intention to Diagnose, Prevent or Treat- Positive. Chronically debilitating and/or life-threatening nature-with approximately 95% of patients with glioblastoma succumb to the disease within 5 years of diagnosis. Number of people affected or at risk-has been estimated to be 0.79 per 10,000.
4	Larotrectinib	Treatment of papillary thyroid cancer	24-Aug-18	11-Jul-19	Intention to Diagnose, Prevent or Treat- Positive. Chronically debilitating and/or life-threatening nature-Unfortunately, 10% to 15% of thyroid cancers will exhibit aggressive behavior. Approximately one-third of patients with differentiated thyroid cancers will have tumour recurrences. Distant metastases are present in about 20% of patients with recurrent cancer and indicate a terminal prognosis. Approximately half of patients with distant metastases die within 5 years. Number of

					people affected or at risk has been estimated to be 1 per 10,000.

Table 6: Showing Orphan designation withdrawal assessment report. [14]

3. Results and Discussion

Orphan drugs Comparison in U.S and E.U:

S. No	Parameter	US	EU
1	Legal framework	Orphan Drug Act (OAD-1983) FDA'SOOPD	Commission Regulation EC No 141/ 2000 EMA, COMP
2	Responsible authority prevalence criteria	Fewer than 2,00,000 persons in the US population	Less than 5, in 10,000 persons in the community
3	The review period of the designation procedure	Typically, 90 days	Maximum of 90-days procedure
4	Annual reports	Should be submitted within 14 months after the Orphan drug designation was granted and annually thereafter until marketing approval	Should be submitted within 2 months following the approved designation
5	Protocol assistance	yes	yes
6	Reduced / waived regulatory fee	yes	yes
7	Tax credits	50% for clinical studies	Managed by the member state
8	Research grants	Program by NIH and other agencies	"FP6" + National measures
9	Marketing exclusivity	Seven years+ 6 months in case of paediatric exclusivity	Ten years+ 2 years in case of paediatric exclusivity
10	Special approval pathways	Fast-track approval Break through therapy Accelerated approval Priority approval	Accelerated assessment (via PRIME) Conditional marketing approval Compassionate use
11	Organization for rare disease	National Organization for Rare Disease (NORD)	European Organization for Rare Disease (EURORDIS)

12	Pricing	Free	Based on member state

Table 7: ShowingOrphan drugs Comparisons in U.S and E.U.

4. CONCLUSION

Governments across the globe have supported the development of orphan disease treatments by providing rewards to pharmaceutical companies by incentivizing them through steps like reduction in procedural fees and giving market exclusivity for certain period after approval of marketing authorization.

The main hurdle to maintain orphan designations after getting the marketing authorization approval is in the demonstration of benefits significance over already approved treatment methods.

The no of orphan designation is facing withdraws the reason being failure on the part of sponsor to provide experimental data to confirm his plan which it can avoid by adequate planning at the design phase itself.

Only in a few countries have orphan pharmaceutical initiatives for rare diseases proven successful. Finding the right incentive structure is challenging in a market with limited first-mover advantages. In addition to the advantages of longer marketing exclusivity periods, waived regulatory fees, subsidies for R&D, tax credits, quick approval, premium pricing, and reduced development times, etc.

Orphan drugs also include challenges like limited scientific knowledge, low number of patients available, high pricing of these drugs & other regulatory challenges.The ODA's enforcement of more orphan drugs has been developed and approved by the US, and in other countries it has similar legislation.

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