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RECENT ADVANCEMENT IN THE FIELD OF ORPHAN DRUGS - A REVIEW

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ABSTRACT

Orphan drugs are the pharmaceutical agents that are being used for the treatment, prevention or diagnosis of rare diseases/condition. The incidence of such diseases has been increasing from the last three decades, which led to the need for developing orphan drugs in pharmaceutical industries. The orphan drug act was passed on 28 January, 1983 under National Organization for Rare Diseases. One of the major drawbacks in the field of orphan drug is that the pharmaceutical industry is not very keen to carry-out research on development of orphan drugs as they do not provide a vast profit to the companies. However, in this review; we have discussed the need, drawback, recent development and future prospective for orphan drugs.

Keywords: orphan drugs, neglected diseases, approved drugs, orphan vaccines.

INTRODUCTION

Orphan drugs are the medicines or vaccines intended to treat, prevent or diagnose a rare condition[1],condition being itself rare[2], e.g. Goucher's diseases, cystic fibrosis, Lysosomal storage diseases (LSD)[3] etc. The World Health Organization defines orphan/rare diseases as, "all pathological conditions that affect 0.65-1 out of every 1000 inhabitants". In Europe countries the rare disease definition is that it affects 5 people in 2,000. Diseases which affect less than 200,000 patients categorized as the rare diseases in USA similarly in Japan those diseases which affect less than 50,000 patients are called as rare diseases[4]. In India, there are around 33 million patients with around 6000-8000 rare condition, mostly genetic in nature. Some diseases like Madras Motor Neuron Diseases and Kyasanur Forest Diseases are limited to India[5]. Sponsors are least interested in producing orphan drugs due to poor market absorbance. In recent years, pharmaceutical industries have been working on development of orphan drugs due to many reasons like the expiration of the patents, competition in the generic market, and increasingly strict regulatory guidelines. According to WHO survey, more than 12 million people are exposed to dog bites, snake bites and scorpion bites out of which 1percent are left treated. The reason behind less treatment is the decreased production of this protective serum or anti venom against these diseases. Pharmaceutical industries developing these orphan drugs have a minimal profit because discontinuous supply of these life saving drugs. And leftover stock of these drugs becomes a burden for the developing countries.

There are approximately 7000 different types of rare diseases and disorders with more being discovered today. It has been reported that there are about 250 new rare cases reported every year, however the acceptable treatment is available only for 200-300 orphan diseases. It is known that the 80% of these rare diseases are of genetic origin and the rest have environmental, bacterial, viral or unknown origin.

Table 1: List of Some Rare Diseases

Acrocephalosynylia	**Acrodermatitis**	**Budd-Chiari Syndrome**	**Behcet Syndrome**
Addison Disease	Adie Syndrome	Carcinoma256, Walker	Bowen's Disease
Alagille Syndrome	Amylose	Charcot-Marie tooth diseases	Brown-Sequard Syndrome
Amyotroph Lateral Sclerosis	Angelman syndrome	Chairi-Frommel Syndrome	Burkitt Lymphoma
Angiolymphoid Hyperplasia with Eosinophilia	Arnold-Chairi Malformation	Colonic Pseudo Obstruction	Caroli Disease
Arthritis,Juvenile Rheumatoid	Asperger Syndrome	Craniofacial Dysostosis	Chediak-Higashi Syndrome

Orphan Drug Law

On January 28, 1983 the ORPHAN DRUG ACT (ODA) was passed in United States with the permission from National Organization for Rare Disorders (NORD)[6]. This Act provided clinical trial incentives to pharmaceutical companies and also gave them market exclusively for 7 years. These incentives resulted in more focused attention of pharmaceutical companies in the area of rare diseases. Following the same policy of US, Singapore (1991), Japan (1993) and Europe (2000) passed the law to promote research and development in the field of rare diseases. European Union provided sell of orphan drug exclusively for 10 years. Other countries like South Korea, New Zealand and India are planning to pass law specific to rare diseases. The orphan act came into consideration after depicting a young boy in US suffering from **TOURETTE SYNDROME.**

Before ODA was passed, FDA approved only 38 drugs with status of orphan drugs, but after passage of ODA that numbers increased significantly. Until May 2010, FDA has approved 353 orphan drugs. After approval of ODA act, the orphan drug approval contributed 17% from 1984-1988 which almost doubled to 31% between 2004-2008. Cancer contributed to 36% between 2000-2006. Many national institutes have come up with aim to identify different generative rare diseases. Institutes like National Organization for Rare Disorders (NORD) and European Organization for Rare Disorders (EURORDIS) collect data on every rare disease reported[7]. At the end, on last day of February Rare Diseases Day is coordinated at the international level by EURORDIS and NORD in the US and other countries.

The FDA Office of Orphan Products Development (OOPD) provides incentives for sponsors to develop products for rare diseases. Humanitarian Use Device (HUD) program designates a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year[8]. The Orphan Products Grants Program

provides funding for clinical research that tests the safety and efficacy of drugs, biologics, medical devices and medical foods in rare diseases or conditions.

Why We Need Orphan Drugs?

If there is no specific treatment for orphan diseases, it leads to psychological distress in patient and its family and also, feeling of hopelessness sets in. There are many diseases which

Lacks specific therapy and there are also some old age unproven therapies and some myths about the treatment of these rare diseases. It was the US who passed the ODA act for research and development in treating rare diseases. The "ORPHAN DRUG ACT" got amended under Federal Food, Drug and Cosmetic Act, 1938[9,10]. Drugs are granted orphan status for a specific indication, and still need studies to demonstrate their safety and efficacy, unless these qualify for accelerated approval.

The major steps regarding the incentives for achieving the orphan drug status (ODS) includes:

- Tax incentives given for clinical research.
- FDA provides assistances for study designs.
- Exemption from application-filling fees.
- Grant given for phase-I and phase-II clinical trials and,
- Marketing exclusivity for duration of 7 years is given after the drug or biological product gets approval[11].

Around 10 million or even more than that patient have been treated by orphan drugs, this data initiate the research against orphan diseases and formation of orphan drug act. Many countries like US, Singapore, Japan, and Europe are working on orphan drugs[12,13]. A group of pharmacologists has appealed to Indian government to in setup ODA in a conference held by the Indian Drug Manufacturing Association in November 2001, but nothing has being done permanently.

Table 2: An assessment of US-FDA approved orphan drugs (as assessed on 01.06.2005 from www.fda.gov/cder/rdmt)

YEAR	TOTAL DRUG APPROVED	APPROVED ORPHAN DRUGS	ORPHAN DRUGS DESIGNATED	PV/TV drug %	SV/TV drug%
1998	30	Lepirudin[PV],Sacrisidase[PV],Rifapentine[PV],Thalidomide[PV],Valrubicin[PV],Thyrotropin-alpha[PV],Modafinil[SV]	7	6/16 (37.5)	1/14 (7.1)
1999	35	Alitretinoin[PV],Temozolamide[PV],Exemestine[SV],Poractant[SV],Nitric-oxide[PV],Benarotene[PV]	6	4/19 21.05	2/16 12.5
2000	27	Gemtuzumab[PV],Arsenic-trioxide[FTA]	2	2/9 (22.22)	0/18 (0)
2001	24	Imatinib Mesylate[PV,FTA],Bosentan[SV]	2	1/7 (14.28)	1/17 (5.88)
2002	17	Nitisinone[PV,FTA],Treprostinilsodium[PV],Sodiumoxylate[PV],Nitazoxanide[PV],Icodextrin[SV]	5	4/7 (57.14)	1/10 10

2003	21	Pegvisomant[PV,FTA],Miglustat[SV], Prussian blue[PV],Bortezomib[PV]	4	3/9 (33.33)	1/12 (8.33)
2004	31	Pemetrened disodium[PV],Cinacalcet hydrochloride[PV],Apomorphine hydrochloride[PV],Azacitidine[PV],L-gkutamine[SV],Pentetate calcium trisodium[PV],Pentetate zinc trisodium[PV],Clofarabine[PV],Lloprost[PV]	9	8/17 (47.06)	1/14 (7.14)
2005	3	None	0	0	0

PV: Priority review orphan drugs = Significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease. **SV**: Standard review orphan drugs = the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs. **PV/TP** drugs: Priority review orphan drugs Vs Total priority review drugs for that year **SV/TS** drugs: Standard review orphan drugs Vs Total standard review drugs for that year. **FTA**: Fast track approval.

Table 3: **Research and Development going in the field of rare diseases/Orphan drugs**

Rare diseases name	**Drug available**	**Marketing authorization holder**
Alzheimer and Parkinson (special condition)	Exelon	Novartis
CCR5-tropic-HIV-1	Selzentry	Pfizer
Chronic Idiophatic Thrombocytopenia	Promacta	GSK
Chronic Lymphocytic leukemia	Arzerra	GSK
Chronic Obstructive Pulmonary Diseases (airflow obstruction)	Arcapta	Novartis
Cryoprinic Associated Periodic Syndrome	Llaris	Novartis
Fabry Diseases	Replagal Fabraenzyme (Agalsidase beta)	Shire Genzyme
Gaucher Diseases	Vpriv Cerezyme(Imigluserase)	Shire Genzyme
Maroteaux-Lamy Syndrome(MPS-VI)	Naglazyme	Biomarin
Mucopolysaccharidosis I(MPSI)	Aldurazyme(Iaronidase)	Genzyme
Non-small cell lung cancer	Xalkon	Pfizer
Non transfusion dependent thalassaemia	Exzade	Novartis
Pancreatic Neuroendocrine tumours	Sutent	Pfizer
Phenylketonuria	Kuvan	Biomarin
Philadelphia chromosome positive chronic myloi leukemia	Tasigna	Novartis
Pompe disease	Mycozyme and Lumizyme	Genzyme
Primary Immune Thrombocytopenia	Rozrolimupab	Swedish Orphan Biovitrum
Restless leg syndrome	Horizant	GSK
Subependymal Giant cell astrocytomas	Afinitor,Votubia	Novartis

Table 4: **Drugs in Development Pipeline**

Diseases	Drugs	Company
Achondroplasia	BMN-111	Biomarin
Cushing disease	SOM230	Novartis
Duchene muscular dystrophy	HGT 4510	Shire
Fabry disease	Amigal	GSK
Homozygous familial Hypercholesterolemia	Kynamro (Nipomersen)	Genzyme
Hunter Syndrome	HGT 2310	Shire
Metachromatic leukodystrophy	HGT 1110	Shire
Pompe disease	BMN-701	Biomarin
Sanfilippo A syndrome	HGT 1410	Shire
Transthyretin familial amyloid polyneuropathy	Tafamidis meglumine	Pfizer

Difficulties in Development of Orphan Drugs: [14-17]

Orphan drugs are those that benefit only a little but intensely needy part of the whole population. These biological products are typically not brought to the market by the pharmaceutical companies due to the low consumption by patients and also, do not satisfy the financial return. As these drugs are mostly used to treat rare diseases of approximately 0.65 populations, they are commonly neglected by the scientific, medical and political communities. The development process for orphan drugs differs from that of other drugs in particular in the clinical phases. It is often especially difficult to conduct the necessary trials for rare diseases because the patients have to be found from all around the world. Because the diseases are rare, the trials also have to be held with far fewer patients.

For the development of orphan drugs a high initial investment war required which could be only balanced when there was a large consumption of the manufactured products to ensure the financial returns. So these drugs were targeted to only those rare diseases, which were found in developed countries, as theses drugs have high cost, so they can be easily consumed only in the countries where the people are economically efficient to buy these orphan drugs as they have high cost. This may also be the reason that India is lacking in development of orphan drugs as the population is very high, the employment is very low and also the consumption of medicines/drugs is mostly by middle cast or other lower cast as compared to the higher casts.

Table 5: Some Orphan Drugs Approved by USFDA (2014)

S.No	Generic Name	Treatment of Disease(s)	Route of Administration	Pharmacological activity
1.	Idelalisib	Chronic lymphocytic leukemia & small lymphocytic lymphoma	Oral use	Phosphoinositide 3-kinase inhibitor
2.	Eliglustat	Type I Gaucher disease	Oral use	Inhibitor of glucosylceramide synthase

3.	Ceritinib	Non-small cell lung cancer which is anaplastic lymphoma kinase(ALK)-positive	Oral route	Anaplastic lymphoma kinase inhibitor
4.	Miltefosine	Leishmaniasis	Oral route	Interaction with membrane lipids inhibition of cytochrome C oxidase
5.	Belinostat	Peripheral T-cell lymphoma	Intravenous route	Inhibitor of histone Deacetylase
6.	Dantrolene sodium	Malignant hyperthermia syndrome	Intravenous route	Activator of catabolism
7.	Tasimelteon	Non-24-hour sleep wake disorder in blind individuals without light perception	Intravenous route	Melatonin MT1 and MT2 receptor agonist
8.	Recombinant human acid alphaglucosidase	Pompe Disease	Intravenous route	Degradation of lysosomal Glycogen
9.	Ecallantide	Angioedema	Subcutaneous route	Suppressor of pathogenetic mechanism caused by mutation of the C1-inhibitor gene.
10.	Siltuximab	Treatment of Castleman's disease	Intravenous route	Inhibitor of IL-6, thus restoring CYP450 activities to higher level
11.	Ramucirumab	Gastric cancer	Intravenous route	Inhibitor of ligand-induced proliferation & migration of human endothelial cells

Orphan Vaccines

In addition to orphan drugs, orphan vaccines have also been developed to control the disease and to prevent the spread of contagious disease. Vaccines are more expensive compared to orphan drugs to treat small number of rare infectious diseases, and for those important but geographically limited diseases (such as arboviral or diarrheal), involving a small number of people. Only eight vaccines registered with orphan status (seven for therapeutic indications e.g., cancer and sickle cell anemia and one to prevent an Asiatic infectious disease - Japanese encephalitis virus), have been developed. Effective vaccine against common infectious diseases like malaria, tuberculosis, and dengue fever,

being still not available , tropical countries have to find their own way to develop/manufacture vaccine facilities[18-19].

CONCLUSION

Orphan drugs are rarely used by the population as the diseases are very rare and are found in approximately 0.65% in the whole world, hence are less manufactured by the pharmaceutical companies. From the review, we conclude that though the rules and act have been passed still there is low manufacturing of orphan drugs by the pharmaceutical companies as the consumption by the patients are very less. Despite the fact that orphan drug act have been passed since 1983, there is still no chances of manufacturing of drugs in India because of low investment by the companies.

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