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Adoption of Orphan Therapeutics

Pharma

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ADOPTION OF ORPHAN THERAPEUTICS

The literal meaning of orphan is the one who lacks support, supervision or care. The term orphan is also used commonly in medical sciences. According to estimates from World Health Organization (WHO), orphan diseases are often debilitating, life-threatening with a prevalence of 0.65%-1%. On a whole these rare diseases affects millions of people globally. Thus Most of the diseases are serious and many of them are even fatal. As the number of individuals affected by a particular disease is small, these poses challenges for development of effective drugs and medical devices to prevent, diagnose, treat, or cure these conditions. The process for developing a new drug or biologic product and bringing it to market is very expensive and lengthy. For orphan drugs which are used to treat rare and neglected diseases, this high-cost, low-success–rate, lengthy model is simply infeasible. focusing separately on rare disease is important because such research may otherwise be diminish when policy makers consider the absolute numbers of people likely to benefit from the investment in research. It is of utmost importance to develop a more integrated approach for rare diseases research and product development. Present review article focuses upon the present scenario of orphan medical products, challenges relating to their research & development and the role of regulatory authority like FDA, EU etc.

ORPHAN IN RELATION TO MEDICAL SCIENCES

The term orphan is also being used in medical sciences. According to U.S Rare Disease Act of 2002, any disease that affects less than 200,000 patients or 1 in 1500 is termed as a rare disease (1,2,3). An orphan drug is defined (1984 amendments of the U.S. Orphan Drug Act) as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the FDA(4,5,6,7).

In European Union, European Medicines Agency (EMEA) defines rare disease as a life threatening or chronically debilitating disease which is of such low prevalence that special efforts are needed to address it." It should affect 1 in 2000 persons (8,9). It also includes some tropical diseases found in developing countries. Besides this there is also a large group of rare diseases that perhaps affect few hundred to a few thousand individuals but are unknown to most including many physicians. Orphan status is conferred when either no satisfactory method of diagnosis, prevention or treatment of the authorized condition exists, or, if such a method does exist, the treatment must be of significant benefit to patients affected by the condition.

Compared to pharmaceuticals, medical devices are an extremely diverse group of products. Although term orphan medical device does not appear in legislative or regulatory language, there are a large number of medical devices that are used generally during complex surgery, anaesthesia, respiratory support, nonsurgical cardiac procedures, administration of certain medications, diagnostic and therapeutic imaging of various kinds, laboratory testing, and other services. Such medical devices for small populations are grouped under the title orphan products in the grants program created by the Orphan Drug Act and are within the charge of the Office of Orphan Product Development (OOPD).

As defined by statute (21 USC 321(h)), a device is: an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

TREND IN THE DEVELOPMENT OF ORPHAN MEDICINES

United States passed its Orphan Drug Act (ODA) in 1983.Under this act pharmaceutical companies are provided with incentives and market is given to them exclusivity for 7 years.

Singapore in 1991, Japan in 1993 and Europe in 2000 passed laws to promote research and development in the field of rare diseases. European Union (EU) gives exclusive rights of selling orphan drugs for 10 years (10). Many Other countries like India, New Zealand, and South Korea are also planning to pass laws specific to rare diseases.

CLASSIFICATION OF ORPHAN IN RELATION TO MEDICAL SCIENCES

Orphan diseases are also called rare diseases. United States and European Union has separately defined them. The drugs used or intended to be used to treat such rare diseases are called orphan drugs.

The broad term "orphan medical product" is used to cover drugs, biologic products, and medical devices. The definition of orphan drugs includes products "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and (except for foods) "intended to affect the structure or any function of the body of man or other animals" (21 USC 321(g)(1)).

FDA also includes biological products in this definition, although drugs are chemically based and biologics are derived

from natural sources such as human cells or microorganisms.

Orphan medical Devices- An orphan medical device is a product that is intended for diagnostic, preventive, or therapeutic use that does not achieve its primary effect through chemical action on the body or through metabolic processes. If compared to orphan drugs, these are extremely diverse group of products. These may be as simple as adhesive bandages to complex one including various cardiac, orthopaedic and neurological implants. There is no requirement of submission of any clinical data before FDA can authorize a device for marketing except for a small percentage of high-risk devices. For such high risk devices manufacturers must submit an approval application that includes safety and efficacy data from clinical trials. This process is complex, high-priced, and lengthy, which may discourage companies from pursuing devices for small populations (11).

One example of orphan medical devices is Vertical Expandable Prosthetic Titanium Rib (VEPTR). It has been approved by US FDA to treat Thoracic Insufficiency Syndrome (TIS) in paediatric population **(**12**)** under Humanitarian Use Device (HUD) programme**.**

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 (13)

Neglected diseases- This term is applied, in particular, to certain tropical infections that are particularly concentrated in some of the poorest countries of the world and that still lack adequate incentives for drug development or mechanisms to make existing treatments available.

IMPORTANT ORPHAN PHARMACOTHERAPEUTIC PRODUCTS (14,15)

TRADE NAME	ACTIVE SUBSTANCE	MARKETING AUTHORIZATION INDICATION
ADCETRIS	Brentuximab vedotin	*Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1. following autologous stem cell transplant (ASCT) or 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. *Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).
ADEMPAS	Riociguat	* Chronic thromboembolic pulmonary hypertension (CTEPH) Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with - inoperable CTEPH, - persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity
ARZERRA	Ofatumumab	* In combination with chlorambucil or bendamustine, treatment of patients with chronic lymphocytic leukaemia who have not received prior therapy and who are not eligible for fludarabine-based therapy. * Treatment of refractory chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab.
BOSULIF	Bosutinib	Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
CYSTADANE	Betaine anhydrous	Adjunctive treatment of homocystinuria, involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylenetetrahydrofolate reductase (MTHFR), cobalamin cofactor metabolism (cbl). Cystadane should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.
DIACOMIT	Stiripentol	Use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.
ESBRIET	Pirfenidone	In adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF).
GAZYVARO	Riociguat	In combination with chlorambucil, treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy.
INOVELON	Rufinamide	Adjunctive therapy in the treatment of seizures associated with Lennox Gastaut syndrome in patients aged 4 years and older.
MYOZYME	Recombinant human acid alpha-glucosidase INN = Alglucosidase alpha	Long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).
ORPHACOL	Cholic acid	Treatment of inborn errors in primary bile acid synthesis due to 3bêta-Hydroxy-delta5-C27- steroid oxidoreductase deficiency or delta4-3- Oxosteroid-5bêta-reductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults.
PROCYSBI	Mercaptamine bitartrate	Treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.

Volume : 4 | Issue : 5 | May 2015 • ISSN No 2277 - 8179

TRADE NAME	ACTIVE SUBSTANCE	MARKETING AUTHORIZATION INDICATION
REVESTIVE	Teduglutide	Treatment of adult patients with Short Bowel Syndrome. Patients should be stable following a period of intestinal adaptation after surgery.
RILUTEK	Riluzole	Treatment of patients with amyotrophic lateral sclerosis. Riluzole extends survival and/or time to tracheostomy
SIGNIFOR	Pasireotide	Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.
SYLVANT	Siltuximab	Treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.
TRANSLARNA	Ataluren	Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.
VIMIZIM	Recombinant human n-acetylgalactosamine-6-sulfatase (INN = Elosulfase alfa)	Treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all
VYNDAQEL	Tafamidis	Treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.
ZOLINGA	Vorinostat	Primary Cutaneous T cell lymphoma

SOME ORPHAN DRUGS APPROVED IN INDIA

The Hyderabad based **NATCO** Pharma's novel anti-cancer drug, **NRC-AN-019** has received " Orphan Drug Designation" from the US-FDA for 3 indications-

1. Glioma
2. Pancreatic Cancer
3. Chronic Myeloid Leukemia

Troikaa Pharmaceuticals, Ahmedabad manufactures following orphan preparations:

1. Tachyban (Adenosine injection)
2. Hemaprot (Aprotinin injection)
3. Neopam (Pralidoxime injection)
4. Narcotam (Naloxone hydrochloride injection)
5. Cyan SOS (Cyanide antidote kit)

CHALLENGES AND PROCESS OF STUDYING ORPHAN

Defining and getting exact epidemiological data about an orphan disease in not as simple. There are difficulties in diagnosing such diseases as well as there are limitations in system of tracking and reporting the diagnosis. Further different countries have different definition for such diseases.

The epidemiological data gathered may help in supporting orphan designation to a drug. The companies looking for such designation must provide a document to FDA indicating that the drug will we used in fewer than 200,000 persons in U.S. Policy makers may also consider the epidemiologic information along with scientific, political, economic, ethical, and other factors for making decisions about the allocation of resources for biomedical research.

The studies regarding natural history of a disease are helpful in determining genetic, environmental, demographic and other variables associated with the disease. They also help us getting information about the phenotypic variations as well as the subtypes of the rare disease. Understanding the natural history of a disease is an important step in the development of therapies.

Various challenges:

Lack of adequate knowledge and training: For most of the rare diseases health professionals often lack appropriate training and awareness to diagnose and adequately treat these diseases

Lack of adequate expertise and review by authorities: there should be adequate expertise at the government agencies that can timely review rare diseases research applications or authorize the marketing of products for rare conditions

Deficient diagnostic systems: For many diseases, there are no proper diagnostic methods. In these cases, diagnosis becomes very difficult. Consequently further steps become problematic.

High cost of "orphan drugs" is an issue: The prices of "orphan drugs" are usually very high. The reasons are quite obvious. Thus affordability becomes difficult. Most of such drugs are rarely available in India. If required these drugs needs to be imported directly in US$ term (16,17) .

ETIOLOGY OF ORPHAN DISEASE

Majority of the rare diseases (80 percent or more) are genetic in origin (see, e.g., NORD, 2007; NIH, 2008). Most of them are caused by defects in a single gene. Multiple different mutations in that single gene may result in disease of varying features or severity. In some rare cases, multiple genes may contribute collectively to manifestations of the disorder. Rare genetic conditions are often inherited but may also arise as a result of sporadic or chance mutations (18).

Some of the rare diseases have infectious cause. Some infections (e.g., those caused by Balamuthia mandrillaris and Chromobacterium violaceum) are thought to be rare worldwide. Others, however, are rare in wealthy countries but common in less economically developed countries

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

It is likely that far more types of poisoning could be listed as rare conditions than are included in the list maintained by the Office of Rare Diseases Research (ORDR) at NIH. Some drugs have received orphan designation and approval for treatment of rare poisonings. For example, FDA has approved an orphan drug for the treatment of acute cyanide poisoning (hydroxocobalamin). Rare conditions may have a variety of other causes. Examples include conditions caused by nutritional deficiencies (e.g., beriberi, which results from thiamine deficiency and is rare in the United States [Medline Plus, 2008] and injuries (e.g., commotio cordis, in which ventricular fibrillation and sudden death is associated

with a nonpenetrating blow to the chest.

PROMOTION OF ADOPTION OF ORPHAN

A) ROLE OF FDA

Policies regarding orphan drug development works mainly under FDA regulations. For any sponsor who is ready to initiate clinical studies of a promising drug, whether for a common or a rare condition, the first step is to file an Investigational New Drug (IND) application. If the results of clinical trials will support FDA approval of a drug, then the sponsor files a New Drug Application (NDA). The FDA then reviews and approves the drug before it can be marketed. For generic drugs, the requirement is for approval of an Abbreviated New Drug Application (ANDA). To get approval of FDA for marketing a drug, sponsors must provide substantial evidence about its safety and effectiveness for its intended use. Data from one adequate and well-controlled study, together with confirmatory evidence obtained before or after that study, can constitute "substantial evidence" of effectiveness for any new drug FDA (Modernization Act of 1997). FDA regulations specify further details about characteristics of adequate and well-controlled studies. FDA has also developed a number of documents that provide additional guidance to industry on the design and conduct of trials to support approval.

Biological products are those which are made from living organisms and may be composed of cells or tissues or of sugars, proteins, or nucleic acids or complex combinations of these substances such as vaccines, antitoxins, therapeutic proteins, and monoclonal antibodies. Most biologics are also drugs and so generally same standards of safety and efficacy are also applied to them as that for the non-biologic drugs. In addition, the incentives of the Orphan Drug Act are available to sponsors of biologics. The Public Health Service (PHS) Act provides Biologics License Application (BLA).Most biologics are approved on the basis of BLA. Title VII of the Patient Protection and Affordable Care Act of 2010 (P.L. 111-148) revised the definition of biological product under the PHS act to include all proteins (except for chemically synthesized polypeptides). In 2003, FDA transferred responsibility for review and approval of most therapeutic biologics from the Center for Biologics Evaluation and Research (CBER) to CDER. The types of products transferred to CDER include most proteins intended for therapeutic use (e.g. interferons, enzymes); agents that modify immune system response (other than vaccines and allergenic products); monoclonal antibodies; and certain other products intended to alter production of blood cells. Depending on the category, some orphan biologics are regulated by CDER and others by CBER. In 2009, FDA issued revised regulations on treatment use of investigational drugs. In general, the agency allows expanded access in three categories of patient populations: individual patients, intermediate-sized groups, and large groups. The conditions that must be satisfied in order to justify expanded use become more extensive as the size of the population to be treated increases. To provide additional resources for FDA and to speed reviews, the Prescription Drug User Fee Act of 1992 (P.L. 102-571) and subsequent renewals and revisions have authorized FDA to collect user fees from companies seeking approval of new drugs (**19).** FDA strongly encourages sponsors of drugs for rare diseases to seek pre-IND meetings to discuss development strategy.

Sponsors of orphan drugs are exempt from user fees, but they benefit generally from the additional resources the fees provide to FDA. For drugs that are intended for use with serious or life-threatening conditions for which unmet needs for treatment exist, FDA has instituted additional options—fast track status, accelerated approval, and priority review—to speed reviews and provide more extensive and timely guidance to sponsors about the nature of the evidence that is needed to support approval. For applications that qualify for fast track status, companies submit modules of an NDA on an ongoing basis for a "rolling review" by FDA as the modules are submitted. In some cases, another option is accelerated approval, which allows the use of surrogate endpoints that are not considered well established but that are determined to be "reasonably likely to predict clinical benefit. FDA then requires post approval studies to develop further evidence about benefits and risks based on clinical outcomes. For priority reviews, FDA sets a goal of completing application reviews within 6 months compared to a standard review goal of 10 months. Another mechanism to facilitate review and, equally important, reduce regulatory uncertainty is the Special Protocol Assessment. It allows FDA to provide expedited assessment of the adequacy of certain clinical trial protocols and to reach agreements with sponsors on the design and size of trials to support efficacy claims in marketing applications. Normally, Special Protocol Assessments are available only after the end of phase II trials. However, for sponsors of drugs for rare conditions, they can be arranged after the end of phase I trials (Anne Pariser, Associate Director for Rare Diseases, FDA, May 14, 2010, personal communication). When FDA grants approval to a sponsor to market a drug, it may specify certain post marketing requirements. As noted above, post marketing studies to develop additional evidence about benefits and risks are required for products approved under accelerated approval procedures. In addition, under the Paediatric Research Equity Act of 2003, FDA may require that companies conduct paediatric studies of drugs, but orphan drugs are explicitly exempt from these requirements. As provided under the Food and Drug Administration Amendments Act of 2007, FDA may also require a post marketing Risk Evaluation and Mitigation Strategy (REMS) if it determines that such a mechanism is necessary to ensure that the benefits of a drug outweigh its risks. A REMS might include (20):

(1) a medication guide to be distributed to patients with each prescription;
(2) a communication plan for educating health care providers; or
(3) one or more elements to ensure safe use.

Before sponsors can apply to have a drug approved under the Orphan Drug Act and before sponsors are eligible for incentives such as orphan products grants, they must apply for and receive an orphan designation for the drug from the FDA's Office of Orphan Products Development (OOPD).

B) ROLE OF EUROPION UNION (EU)

In the *European Union*, following benefits are given to the companies with an orphan designation for a medicinal product:

- Benefit from incentives by protocol assistance (scientific advice during the product development phase).
- Exclusive marketing authorization for 10-years.
- Financial incentives in terms of fee reductions or exemptions and national incentives.

Since 1 January, 2007, orphan medicinal products are eligible for the following level of fee reductions:

- 100% reduction for protocol assistance and follow up;
- 100% reduction for preauthorization inspections;
- 50% reduction for new applications for marketing authorization;
- 50% reduction for post-authorization activities, including annual fees (applies only to small and medium sized enterprises), in the first year after grant of a marketing authorization.

In 2007 USA and European Union took a decision of common application procedure for orphan drugs, so as to make easier and less time consuming for pharmaceutical companies to apply for Orphan drug approvals in both the regions

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C) INDIAN SCENARIO

Worldwide over 350 Million people are affected by rare diseases including 30 Million in USA, 30 Million in EU,31 Million in India.

In India rare disease population is estimated to be around 72,611,605(21).

Organization for Rare Diseases India (ORDI) launched on 18th February 2014. ORDI was founded to address the many challenges in the management of rare disease in India. Like many developing countries, in India currently there is no standard definition. ORDI suggests a disease to be defined as rare if it affects 1 in 5,000 people or less. Lack of awareness about rare disease even among doctors means that a diagnosis can often take many years. The cost of diagnosis and treatment can also be prohibitively expensive. In the absence of any national government policy for rare disease, there is no push for the development of orphan drugs.

There are numerous disease-specific organizations in India, including groups like the Down Syndrome Federation, the Pompe Foundation, and the Lysosomal Storage Disorders Support Society. However, until now, there has been no group serving as the collective voice of and advocate for rare disease patients throughout the nation. ORDI was formed to address the unmet needs of rare disease patients in India. It will serve as an umbrella organization for rare disease patients and other stakeholders throughout the country. The ORDI team consists of experts in genetics, molecular diagnostics, drug development, bioinformatics, communications, information technology, patient advocacy, and public service (22).

A group of pharmacologists at a conference held by the Indian Drugs Manufactures Association in 2001 requested the Indian Government to institute the Orphan Drug Act in India (23).

In India on February 28th, 2010 rare disease day was first observed with support of LSD support society of India. In 2012, 29th February was observed as rare disease day. In India it was organised in Mumbai.

In 2015, 20th February is observed as a rare disease day.

About 6000-8000 rare diseases, mostly genetic in nature have been identified in India. Examples include addition's disease, ichthyosis retinitis pigmentosa, etc., It was initially estimated that over 31 million Indians are suffering from rare diseases in the country; many of these diseases still do not have any cure. Taking the lower limit of global prevalence estimate, populous nations like India and China should have more than 70 million rare disease cases each.

As stated above, 1983 signaled the importance of "orphan drugs" with the ODA in the US and later by Japan, EU, and Australia. Following similar footsteps, India should also encourage its domestic pharmaceutical industry to get engaged in research to discover drugs for rare diseases by putting an "ODA" in place, extending financial support, tax exemptions and regulatory concessions like smaller and shorter clinical trials, without further delay

CONCLUSION

The new business model of orphan drugs offer an integrated healthcare solution that enables pharmaceutical companies to develop newer areas of-

Therapeutics
Diagnosis
Treatment
Monitoring and
Patient Support

In India, enough awareness has still not been created to address these challenges, despite publication of several rare disease case reports in the peer reviewed journals and existence of a number of support groups.

The Government of India should visualize this scenario sooner, and come out with an appropriate ODA combating the challenges, hence the domestic pharmaceutical industry of India, in general and biopharmaceuticals industry of the country, in particular, will be able to emerge as a force to reckon with, in this important global space, much faster than what one would currently anticipate. Such legislation could also bring relief to the unlisted very possibly large groups of rare diseases suffers, in India.

Government should also develop a comprehensive action plan for rare diseases research that covers all institutes and centers and that also defines and integrates goals and strategies across units. This plan should cover research program planning, grant review, training, and coordination of all phases of research on rare diseases

Following similar footsteps as USA & EU, India should also encourage its domestic pharmaceutical industry to get engaged in research to discover drugs for rare diseases by putting an "ODA" in place, extending financial support, tax exemptions and regulatory concessions like smaller and shorter clinical trials, without further delay

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