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ORPHAN DRUG - THE CURRENT GLOBAL AND INDIAN SCENARIO

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ABSTRACT

It was not until a few decades ago that orphan drugs, still 'enjoyed' the status of pharmaceutical touch-me-not entities. However, the past two decades have witnessed a radical shift in the approach of global pharmaceutical industry towards orphan drug. They are usually not studied for their pathophysiology or for newer therapeutic options, as they are not economically viable. In previous decades, rare diseases were nearly invisible in national health care systems. Due to lack of knowledge on these very rare and complex diseases, patients, families and careers were in the dark and faced extreme difficulties in accessing a diagnosis, appropriate care and treatment. Then a guideline (orphan drug act-1983) for orphan drugs has been made in the USA. In 2001 a conference was held by the Indian drugs Manufactures association (IDMA), where a group of pharmacologist requested the Indian government to establish the Orphan drug act in India. The percentage of patients suffering "rare diseases" in India is reportedly higher than the world range but the production of orphan drugs are low as compared to that of developed countries like US, Europe. The present studies review the current global and Indian scenario of orphan drugs.

INTRODUCTION

Diseases that manifest in patient populations representing at the maximum 6-8% of the world population are defined as the "rare diseases" or "orphan diseases." An orphan drug is a pharmaceutical agent that is used to treat a rare medical condition (*viz.*, glioblastoma multiforme, nocardiosis, tourette syndrome etc.,), the condition itself being referred to as an Orphan Diseases.[1] The term "orphan diseases," broadly speaking is attributed to disease that affects only a small number of patients (so- called health orphans).[2] The world health organization defines orphan diseases as 'all pathological conditions that affect 0.65-1 out of every 1000 inhabitants.' The EU defines a rare disorder as one with a prevalence of 5:10,000 Europeans; the USA accepts it as an ailment affecting fewer than 2, 00,000 Americans. Japan has the limit at 50,000 Japanese patients and Australia at 2000 Australian patients.[3] Paradoxically, though rare diseases are of low prevalence and individually rare collectively they affect a considerable proportion of the population in any country.[4] There are approximately 6,000 orphan diseases, out of which 80% are genetic.[5] Most rare diseases are genetic; because symptoms do not appear earlier they exist throughout the person's entire life. However, rare diseases can strike at any point in a person's lifetime, leaving them with crushing health worries, disability, and often exorbitant medical bills from mostly incurable conditions.[6] Some of the rare diseases can be occurring due to allergies or infections (bacterial or viral) or due to proliferative and degenerative causes, for example the rare genetic diseases Ribose-5-phosphate isomerise deficiency has been diagnosed in a single patient only.[7] The United States was the first country introduced an orphan drug act in 1983, after that number of other countries has followed the program, for example Japan (1993), Singapore (1997), Australia (1998) and the EU (2000). In Europe Union acts were made much later than the USA because it is group of 28 countries and its capabilities regarding the health is very much dispersed.[8]

However, in the recent years, faced with an apparent innovation crisis in the R&D sector, increasing drug development costs, increasingly stringent regulatory guidelines leading to massive decline in the drug approvals and decline of the "blockbuster model" of drug development, the pharmaceutical companies are now exhibiting a shift in drug development strategies and are being seen to pursue the rare and orphan disease markets very aggressively. Orphan diseases have not only captured the scientific community's imagination but also the interest surrounding them has spilled over to the general public, especially in developed countries during the last few decades.[2] Unfortunately, in developing countries like India, there still exists a lack of awareness not only among the general public but also medical practitioners and the concerned authorities as well. Hence, in this review, it is our attempt to shed light on the current global and Indian scenario with respect to orphan drugs.[9]

Concept of Orphan Drug

Medical melodrama in the early 1980's in the US set the pace for the concept of Orphan Drug and its regulations. It depicted a young boy with Tourette syndrome, which generated the public opinion for unfortunate victims of these diseases. With this issue in the public, the Orphan drug bill was passed in 1981, but the US congress stalled it [3]. A specific treatment of the orphan condition was not lucrative for the pharmaceutical industry, as these medicines would be used only by a small number of patients. There is a 13-fold greater chance of a medicine being brought to market for central nervous system disorder or cancer, than for a neglected disease.[10] There was no incentive for the pharmaceutical industry to spend time and money on unproductive ventures. Moreover, research had to be prioritized to make best use of available resources. This gave rise to the concept of Orphan drugs which lack sponsorship, are expensive to investigate and develop, are used by few patients and bring inadequate rewards therefore there is very little incentive for marketing these.[3]

"Orphan drugs" – Denotation in various boundaries

United States

As defined in the United States, any drug developed under the Orphan Drug Act of January 1983 (ODA) is an Orphan Drug. The ODA is a federal law concerning rare diseases (orphan diseases) that affect fewer than 200,000 people in United States or are of low prevalence (less than 5 per cent 10,000 in the community).[11]

Europe

A disease or disorder that effects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan drug regulation 141/2000). At first glance, this may seem a small number, but by this definition, rare diseases can effect as 30 million European Union citizens. According to EURORIDS (European Organization for Rare Diseases), the number of rare diseases numbers from about 6,000 to 8,000, most of which have identified genetic conditions, with medical literature describing approximately five new rare conditions every week. Twenty-five to Thirty million people is reported to be affected by these diseases in Europe.[11][12]

Japan

A drug must meet the following three conditions to be considered for orphan drug designation in Japan. Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan's definition of rare. The drug treats a disease or condition for which there are no other treatments available in Japan or the proposed drug is clinically superior to drugs already available on the Japanese market. The applicant should have a clear product development plan and scientific rationale to support the necessity of the drug in Japan. Once clinical trials are completed, a New Drug Application (NDA) can be submitted. It is important to keep in mind that while Japan has orphan drug legislation, this legislation has room for interpretation. The MHLW (Ministry of Health, Labour, and Welfare) makes orphan drug designation and approval decisions on a case-by-case basis. This is especially true when determining the number of Japanese clinical trials required for approval.[12]

Australia

The Therapeutic Substances Regulations does not define a rare disease or orphan indication regarding the number of patients, but rather indicates that it must not be intended for use in more than 2000 patients a year if it is a vaccine or in-vivo diagnostic. To attain the orphan designation, "the application must show why the medicine is an orphan drug." In Australia, orphan drugs are drugs used to treat diseases or conditions affecting fewer than 2,000 individuals at any one time (0.2%).[11][12]

India

The need for such an act is thus evident from the initiative by the Indian Pharmacists and the Government to implement Laws, which would strengthen the health infrastructure and provide relief to the numerous rare disease sufferers throughout the country. A group of pharmacologists at a conference held by the Indian Drugs Manufacturers Association in 2001 requested the Indian Government to institute the Orphan Drug Act in India.[11]

The International scenario

Rare diseases have increasingly been discussed in the media over the past several years as the number of new treatments has surged. Many of these diseases are life-threatening or life-limiting, and while some conditions can now be treated and managed as chronic conditions, for the first-time new curative treatments are bringing the prospect of a better life to patients. This report updates an analysis of the Orphan Drug market published by the Institute in October 2017 and provides a historical perspective on the characteristics of rare diseases, their treatments and the role of the Orphan Drug Act of 1983 in advancing rare disease medicines. It describes the characteristics of orphan drug spending, volumes and prices, placing orphan drugs in the context of specialty drug trends and overall medicine spending levels and growth.[13]

The main regulatory approaches to orphan drugs can be distinguished by comparing the economic and the societal perspective on the 'equality' of healthcare policies. A matrix can be built representing the current dominant approaches identified in table .1, highlighting the relevance of the societal and economic perspectives. The matrix shows that, while the European approach is characterized by greater attention to both the societal and economic perspective given the high interest in market regulation. In the Asian approach, however, the focus is more on the societal perspective given the high interest shown in community well being. In the African-Oceanian approach, dominant attention to social well being or market interest does not emerge. Evidently, in

each country's regulatory approach, the dominant culture of the country is revealed.[14]

Table 1: A matrix representing of dominant regulatory approaches to orphan drugs and rare diseases.[14]

				Relevance of the societal perspective	
				high	**low**
Relevance of the economic perspective	**low**			E.g., European Approach	E.g., American Approach
	High			e.g., Asian approach	e.g., African and oceanian approach

United States

The US ODA passed in 1983 and subsequently amended in 1984, 1985, 1988, 1990 and 1992, was distinctly brought out to prioritize the treatment of around 25 million American victims of orphan diseases.[2] Many rare diseases remain without effective treatments despite over 500 orphan drug therapies having been approved in the United States. However, a growing focus by researchers and the FDA on rare disease therapies have resulted in a dramatic increase in the number of new therapeutic options for these patients over the past two years. In 2017, the FDA approved 80 orphan indications and in 2018, it approved 57 in the first eight months of the year. The combination of scientific advances, along with a growing commitment by policy makers to advance precision medicine, is fuelling the increases number of orphan therapies.[13]

Orphan drugs can be expensive for patients and payers. However, there is generally an inverse relationship between the price of these therapies and their volume of use, given that orphan drugs are developed for small patient populations. Although the median annual cost for an orphan drug in 2017 was over $46,800 the median annual cost for the top ten rare disease therapies used by the greatest number of patients was much lower at $1,216. Overall, drug spending in the United States is evolving from an emphasis on high-volume but with higher value in terms of patient outcomes.

The orphan drug share of the total volume of pharmaceuticals used in the United States declined from a peak of 0.6% in 2003 to 0.3% in 2015 but has risen to 0.4% by 2017. Total drug spending in the United States in 2017 was $451 billion, with almost 56% spent on non-orphan traditional drugs, 34.7% spent on non-orphan speciality drugs and 9.6% spent on orphan indications of approved orphan drugs. Spending on orphan indications has increased moderately and these drugs represent only a small part of the overall medicine budget.

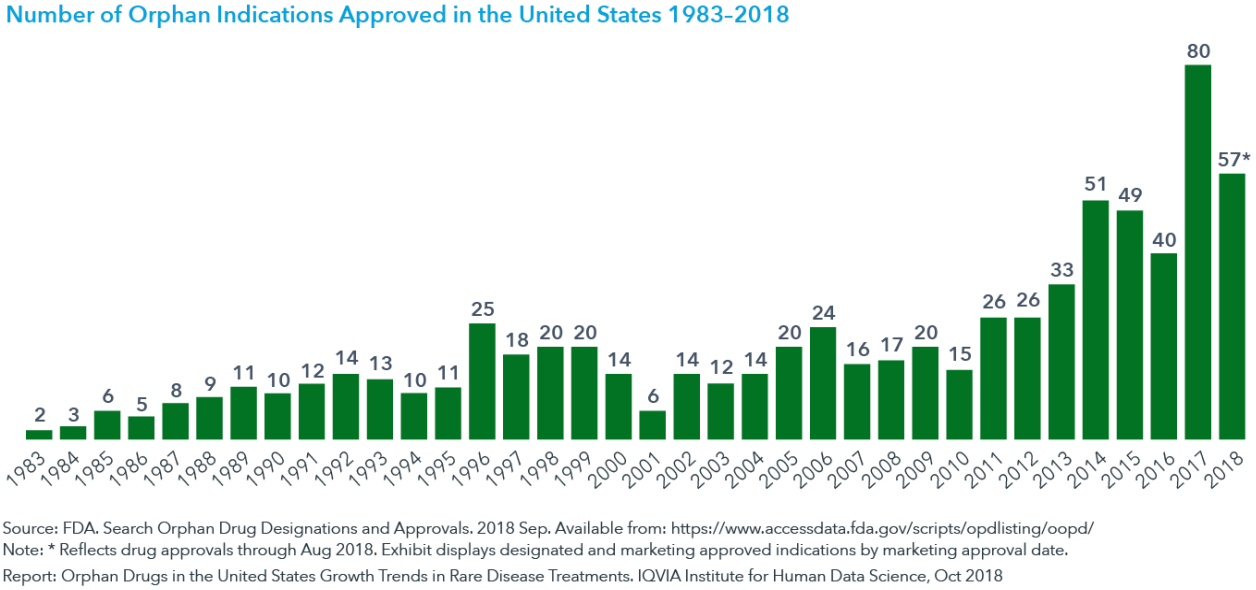
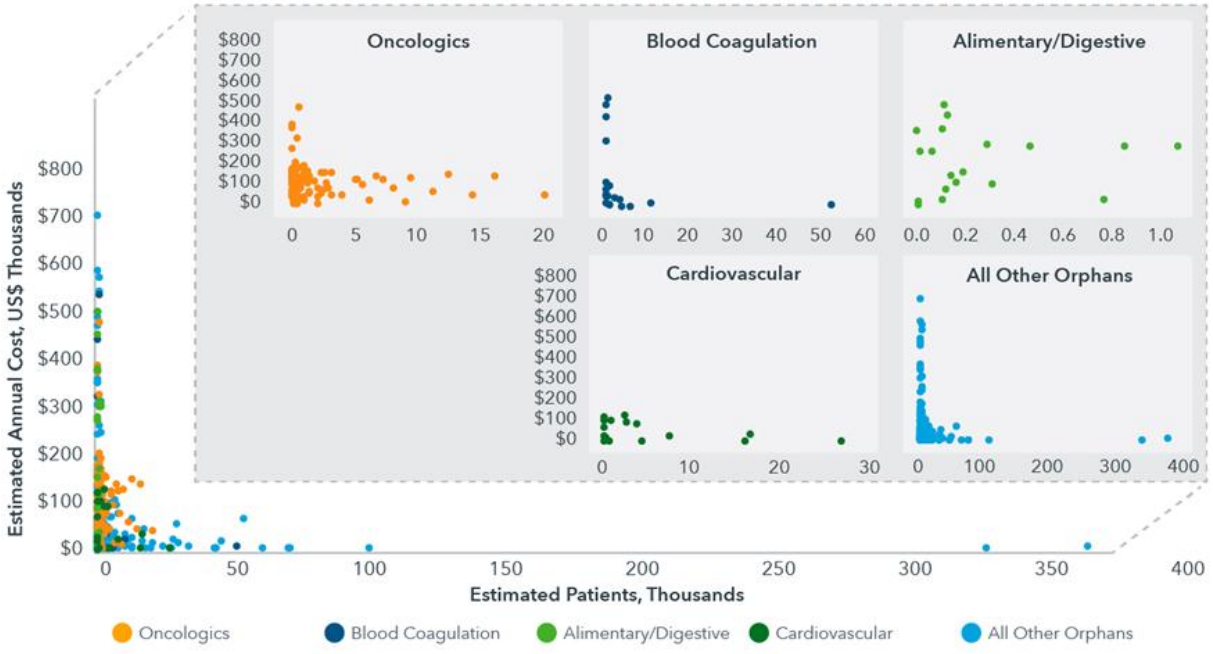


Fig: 1. Since The Passage Of The Orphan Drug Act, The Number Of Orphan Indications Approved In The United States Has Risen Dramatically.

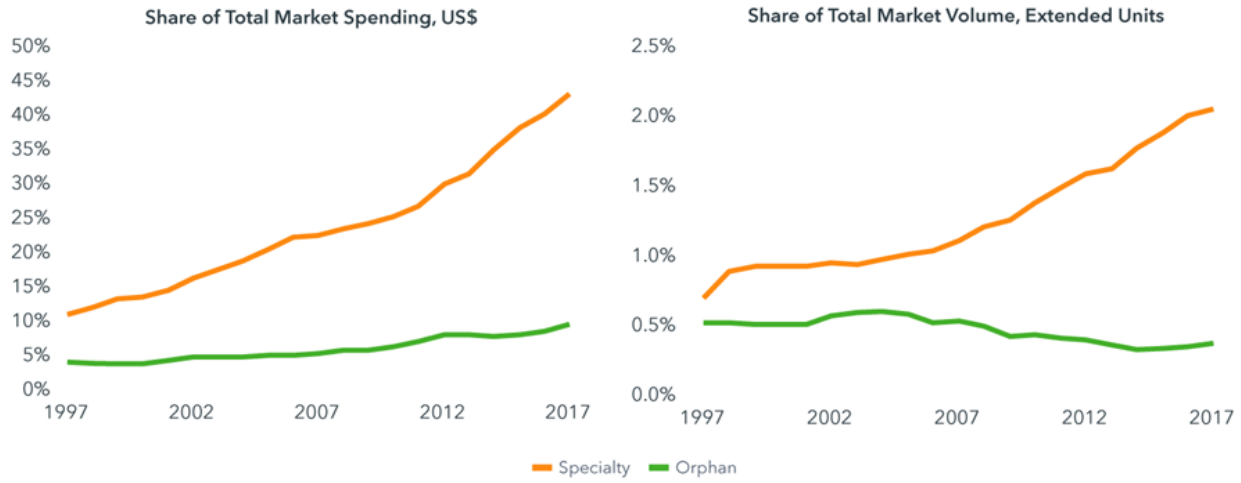
The FDA approved 80 new orphan indications in 2017 and 57 just within the first eight months of 2018, the highest numbers annually since the passage of the Orphan Drug Act. The FDA granted orphan designations to over 429 unique drugs under development in 2017. Drug manufacturers continue to increase their focus on the development of therapies for orphan indications and half of the 42 new active substances (molecules not previously approved as a medicinal product) launched in the United States in 2017 were orphan drugs.



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018
Note: Though scales vary, all x-axes of charts within the zoom box display the number of patients in thousands.
Report: Orphan Drugs in the United States Growth Trends in Rare Disease Treatments. IQVIA Institute for Human Data Science, Oct 2018

Fig: 2. Orphan Drugs That Are Used To Treat Small Populations Are Often More Expensive Than Orphan Drugs Used For Larger Populations.

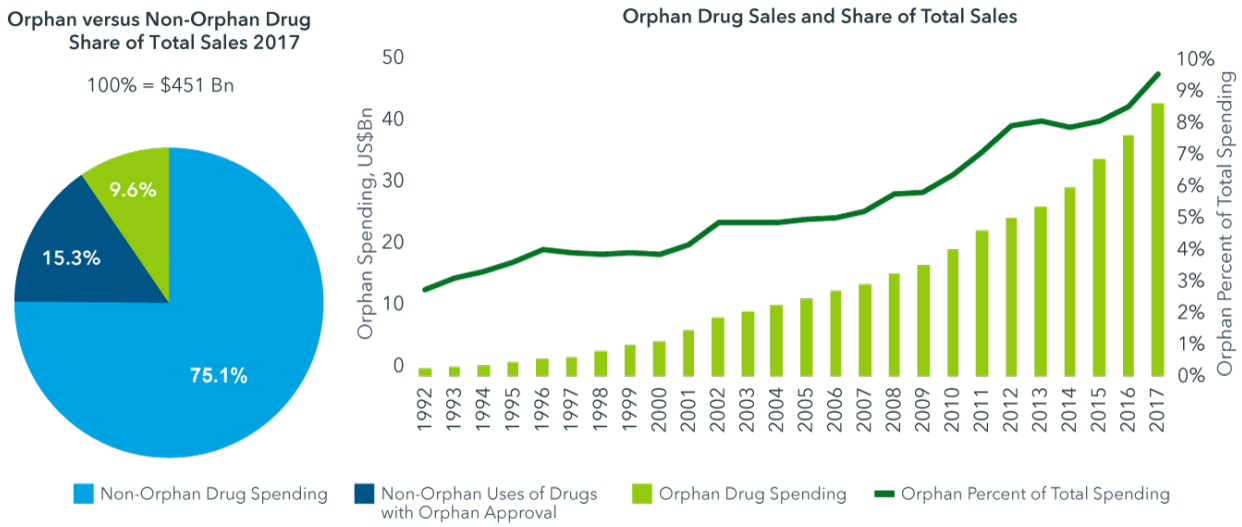
An inverse relationship exists between the cost per year for a therapy and the number of patients, with more expensive therapies being dispensed to relatively few patients. The median annual cost for an orphan drug in 2017 was over $46,800 per year. However, the ten orphan therapies used by the greatest number of patients averaged $9,676 per year (the median cost was $1,216).



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018
Notes: Specialty and orphan shares are based on total market spending or volumes. Specialty and orphan segments overlap, however, some orphan drugs are considered traditional using IQVIA's specialty pharmaceutical definition. Extended units refer to the smallest dose unit of a medicine, typically a pill, vial, or ampoule.
Report: Orphan Drugs in the United States Growth Trends in Rare Disease Treatments. IQVIA Institute for Human Data Science, Oct 2018

Fig: 3. Medicine Spending In The United States Is Shifting From Traditional Small Molecule Drugs Towards Specialty Medicines That Treat Relatively Few People With Chronic, Complex Or Rare Diseases.

Specialty share of total medicine spending has risen from 11% in 1997 to 43% in 2017, while spending on orphan drugs has risen from 4% to 10% during the same period. Many orphan drugs are specialty products, and 87% of orphan spending falls within specialty. The evolution of drug spending has been accompanied by cost-saving mechanisms introduced by healthcare stakeholders including: specialty tiers in health plans, patient co-insurance payments, use of specialty pharmacies and limited distribution networks, among others, that increase the cost burden on patients.



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Accessed Sep 2018
Note: Volume is based on Extended Units. Orphan drug spending includes only orphan approved uses of drugs with orphan approvals.
Report: Orphan Drugs in the United States Growth Trends in Rare Disease Treatments. IQVIA Institute for Human Data Science, Oct 2018

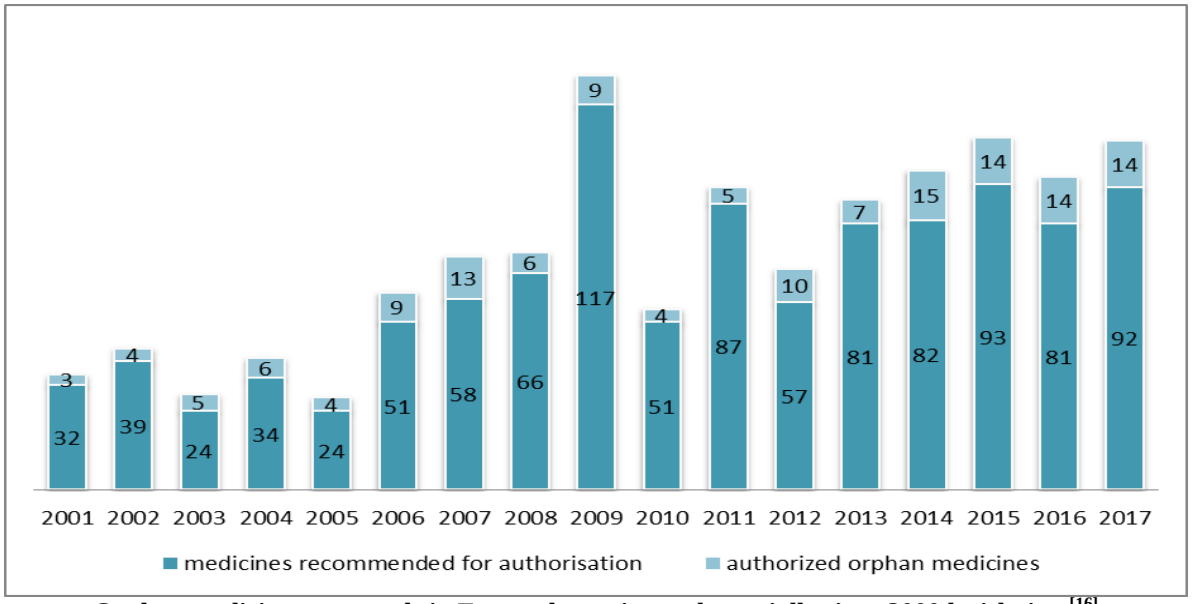
Fig: 4. Although A Quarter Of All Drug Spending In The United States Is Tied To Drugs With Orphan Approvals, Only 9.6% Of Their Use Is For Orphan Designated Indications.

While the number of approved orphan drugs increased from 364 in 2013 to 487 in 2017, the share of total drug spending tied to orphan indication use increased from 8.1% to 9.6%, up from about 3% in 1993. Non-orphan use of these molecules represents 15.3% of overall medicines spending, reflecting that for those molecules with both orphan and non-orphan indications, the non-orphan indications represent much of their use and sales. Use of orphan drugs for their approved orphan indications account for approximately $43 billion.[13]

By the provision of huge amount of incentives, the most prominent of which includes exempting the designated orphan drugs from paying new drug application fee, waivers for post approval annual establishment and products fees, provision of tax credits on clinical research as well as exclusive marketing rights for up to the period of 7 years, ODA has become a huge success story that has set the benchmark for other countries worldwide.[2]

Europe

Owing to the complexities that arise from the differences in the competencies of the various countries constituting the EU, multiple articles, spanning a number of years, demonstrate that Europe has an integrated, multi-country approach to rare diseases.[15] Regulatory guidelines regarding orphan drugs took some time to come into existence. However, the joint efforts at national and European levels, especially by the EMEA, finally bore fruit on 16 December, 1999, when the European parliament and council successfully framed the orphan drug regulations. A dedicated committee of orphan medicinal products within the EMEA, comprising persons appointed by the European member states, European commission and patient associations, was formed with the goal of examining the orphan drugs applications and aiding the commission in discourses over orphan drug.[2] Europe has also developed the European project for rare disease National plan (EUROPLAN) to facilitate the creation of national plans in the region.[15]



Orphan medicines approvals in Europe have risen substantially since 2000 legislation.[16]

Table 2 : US **and EU orphan designations per year 2010-2014.**[7]

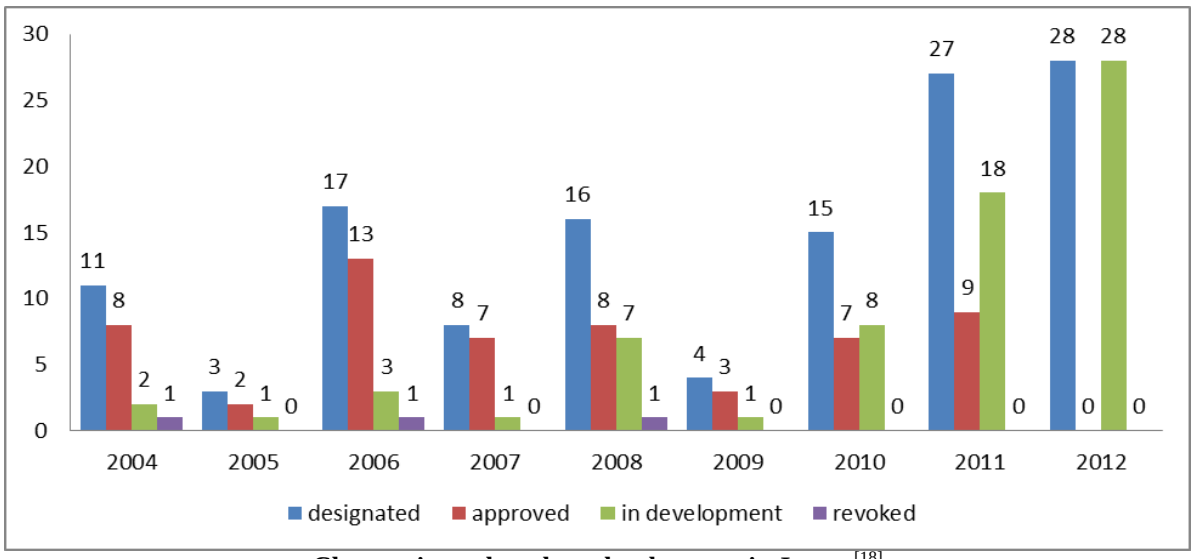
Year	Designations per year		Growth per year	
	USA	EU	USA	EU
2010	195	130	+18%	+19%
2011	202	108	+4%	-17%
2012	190	149	-6%	+38%
2013	260	124	+37%	+17%
2014	291	201	+12%	+22%

Japan

Almost 10 years on since the development of US-ODA, Japan, on 1 October 1993, came up with its own set of orphan drugs regulations by induction of few special provisions aimed at promoting R&D in the field of orphan drugs.[2] Japan has policies promoting orphan drug research and development. For instance, it has pharmaceutical affairs law (PAL) encourages research that examines orphan drugs.[17]

The new provisions in the Japanese guidelines suggested that the status of orphan drugs could be accorded to only those that would fulfil the below listed 2 criteria:

1. The target disease would have to be either an incurable one with no existing treatment or the expected efficacy and safety of the new drug would have to surpass the already existing ones.
2. The number of afflicted patients would have to be below 50,000 translating into an incidence of 4 per 10,000.[2]



Changes in orphan drug development in Japan.[18]

IMPACT OF ACTS: ORD IN US, EU AND JAPAN

Since the ODA was passed in 1983, more than 400 ODs have been developed and marketed in the US which suggests that the incentives are having an effect. Moreover, the last 10–15 years have been the most successful period in the development of ODs. According to FDA, nearly 200 ODs enter development each year and approximately one third of new drugs approved by the FDA are for the treatment of RDs. Since 1983, a total of 177 approvals have originated from 1,391 ORDs to treat rare cancers, which represents 36% of all approvals within the U.S. ODA.[5] ODA incentives are also credited with contributing to the 'breakthrough innovation' that provides advantages over previously available therapies.[19] New patents and additional exclusivities grants help in protecting these drugs beyond their ODE periods.[20]

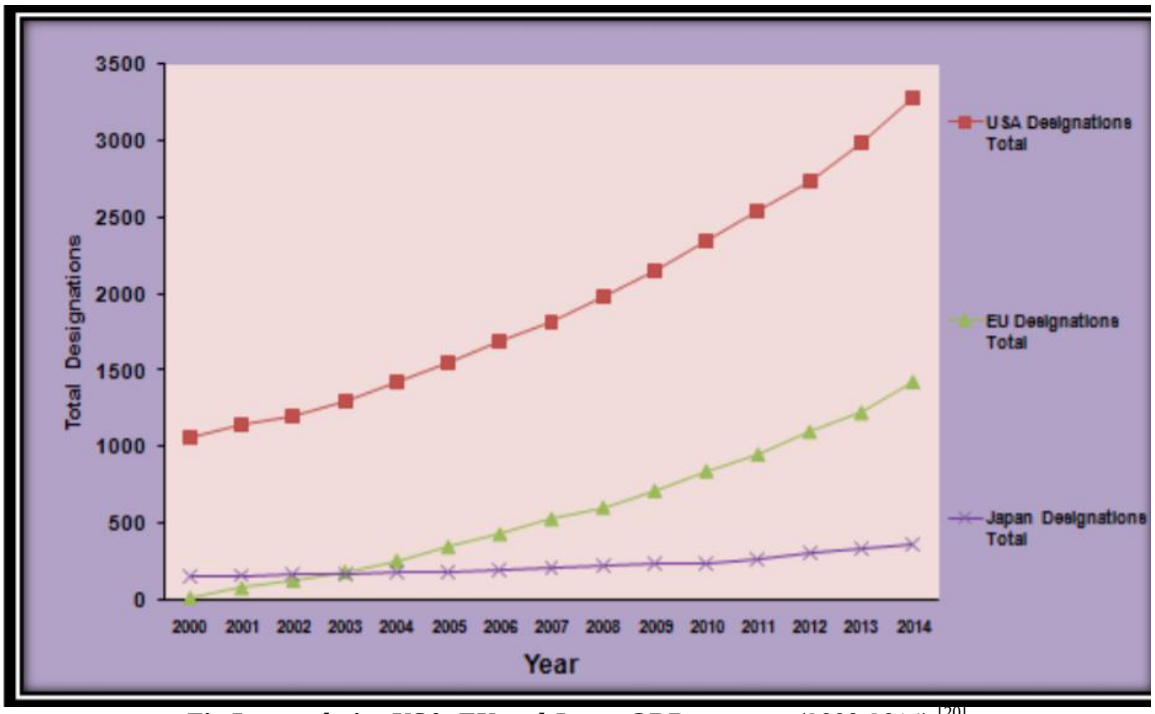


Fig 5: cumulative USA, EU and Japan ORD per year (2000-2014**).**[20]

Scenario in India

In India, there are nearly 70 million people (1 in 20 Indians) affected with a rare disorder. In the state of Karnataka alone, there are around 30-40 lakhs affected persons.[20] About 6000-8000 rare diseases, mostly genetic in nature have been identified in India.[1] Most of the diseases are genetic in nature and do not have any treatment. The scarcity of regulation of orphan drugs adversely affects the economic growth of Indian medicinal industries.[7]

Cystic fibrosis was thought to be very rare in India, but genetic analysis has now shown that the disease in prevalent but was undiagnosed earlier. India has reportedly higher rare disease population than the world average, but initiatives from government side are still less[21], and in fact, India lacks legislation for orphan medicines and rare diseases, in spite that these are most populated countries.[22]

Globally as well as in India, rare diseases pose a significant challenge to public health systems in terms of- difficulty in collecting epidemiological data, which in turn impedes arriving at burden of diseases and cost estimations difficulty in research and development, making correct and timely diagnosis, complex tertiary level management involving long term care and rehabilitation and unavailability and prohibitive cost of treatment.[4]

Table 3: Rare diseases list in India.

Disease	Per 100,000	Total Indian population
Acatalasmia	3	36,000
Acromegly	5	60,000
alkaptornuria	0.3	3,600
Alpa – 1 antritrypsin	25	300,000
Grave disease	50	600,000
Parkinson disease	15	180,000

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

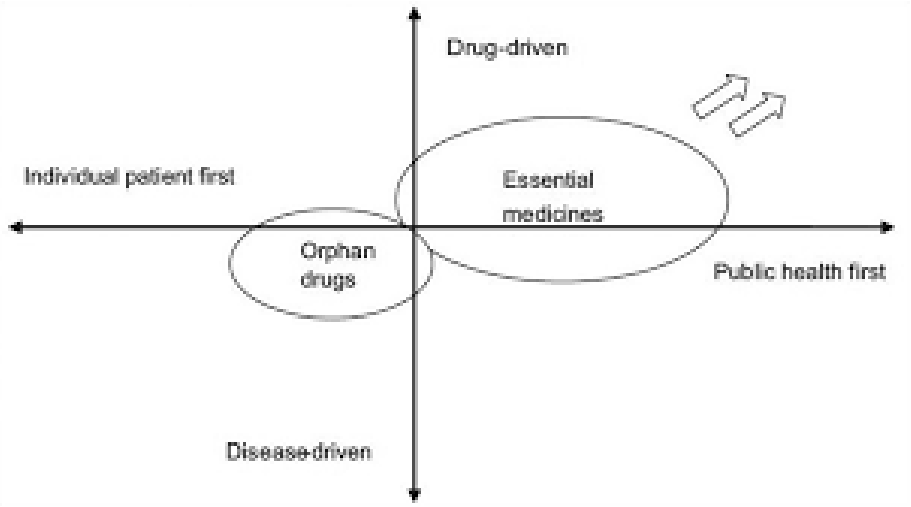


Fig: 6 drug driven refers to more emphasis on the drug compound for decision-making. "Diseases driven" refers to more emphasis on the characteristics of the disease making process. The arrows indicate a future trend based on recent developments.[1]

With its huge population and wide spectrum of disease, India can provide considerable advantages:

- Extensive population
- Wide variety of disease including many rare and ultra rare diseases
- Developed medical practices
- English as official language used in medical records, hospital administration and regulatory administration
- Cost efficiencies associated with resources leading to lower development costs
- Experienced investigations and clinicians
- Rapid enrolment leading to lower development costs
- Fast regulatory timelines and simplified regulatory process
- Exemption in excise duty and service tax on clinical research services offers a further financial incentive
- Quality and GCP guidelines compatible with international requirements
- Huge work force availability.[23]

Rare diseases demand a comprehensive policy response, which India has been weak in offering. And a critical reason for that is funding.[6] Currently drug developers in India are receiving no formal incentives from the government and hence are more focused on developing affordable drugs for more common diseases such as oral insulin, statins for preventing or slowing the progression of cardiovascular diseases, vaccines and antibiotics for a number of preventable infectious diseases.[24]

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 disease by putting an ODA in place, extending financial support, tax exemptions and regulatory concession like smaller and shorter clinical trials, without further delay.[1]

The reasons to adopt a national plan for rare diseases are

1. Recognize and address the specificities of rare diseases in a comprehensive manner by setting up a political and legal framework, involving all stakeholders, and coordinating all relevant actions at the national and regional level in the following areas:

- Access to care, notably structuring national healthcare provisions to facilitate access to experts for adequate diagnosis, therapies and care and define healthcare pathways for people living with a rare disease;
- Access to adapted social services with the implementation of adequate connections between relevant and existing healthcare services and social services;
- Stimulate and support innovative research at national level;
- Identification, development and support of rare disease patient registries;
- Participation in European and international research;
- Participation in European innovative policies on rare diseases.

2. Map out medical expertise on rare diseases across the country. Enable the adoption of an official process to accreditate Centers of Expertise, in charge of providing adequate diagnosis and care through multidisciplinary teams of experts as well as doing clinical research; and enable the participation of Centers of Expertise in the current European Reference Networks on rare diseases.

3. Identify and establish social services and programs relevant to rare diseases (resource centers, disability programs, specialized trainings for professionals involved in diagnosing and management of rare diseases), and bridge the gaps between different services through case management.
4. Better integrate the European legislations (e.g. orphan drugs, pediatric drugs, advanced therapies, clinical trials, cross-border healthcare, European Pillar of Social Rights) and European Policy Recommendations into the national healthcare and social systems, including those adopted by the EU Committee of Experts on Rare Diseases/ European Commission Expert Group on Rare Diseases.
5. Recognize the added value of rare disease patients' organizations and National Alliances as key partners, bringing in their expertise on dealing with the rare disease on a daily basis, and involve them in decision making committees and programs dedicated to rare diseases in the fields of research, healthcare and social care.
6. Balance budget and ensure a financial sustainability of the plan by defining a series of specifically funded measures and actions for improving medical and social care for people living with a rare disease.[25]

Challenges faced by orphan drugs

- These challenges include difficulties in attracting public and private funding for research and development
- Challenges in assessing clinical relevance and cost effectiveness: recruiting sufficient numbers of research participants for clinical studies, appropriately using clinical research designs for small populations.
- Lack of knowledge and training: for many rare diseases, available information is inadequate. Health professionals often lack appropriate training and awareness to be able to diagnose and adequately treat these diseases.
- Lack of adequate expertise and review by authorities: securing adequate expertise at the government agencies that review rare diseases research applications or authorize the marketing of products for rare conditions.
- Deficient diagnostic systems: for many diseases, no diagnostic methods exist, or diagnostic facilities are unavailable. In these cases, diagnosis may be problematic consequently; validity, coding and reproducibility are problematic. Although the pace of gene discovery for rare genetic diseases has accelerated during the past decade, in part, due to the success of the human genome project, translation of these discoveries to clinical utility still lags behind
- High price of "orphan drugs" is an issue: for obvious reasons, the prices of orphan drugs are usually very high, some even costs as high as US $ 400,000 annually and thus beyond affordability of many who are outside the purview of any drug price reimbursement scheme. Most of such drugs are rarely available in India and there is no reasonably affordable "rupee" price for these drugs directly in US$ term, unless Indian policy makers wake-up some day and take appropriate measures in this important area.[26]

Some latest initiatives taken in India are

May 15, 2016:

Rare Disease Patients Make a Fervent Appeal to Government Patients suffering from rare mucopolysaccharidoses and other RD and their families came together to appeal to the state government for providing treatment on the occasion of International Mucopolysaccharidoses (MPS) Day. The event was organized by Lysosomal Storage Disorder Support Society (LSDSS) and ORDI.

Apr 8, 2016:

The First Draft Rare Disease Policy by the Karnataka Government. The draft framework is jointly prepared by highly expertise of India in collaboration with Center for Health Ecologies and Technology (CHET) Bangalore. The draft is based on EU's recommendation on the action for RD, focusing on prevention, diagnosis and screening of disorder, access to treatment, multi-disciplinary care, research, and access to information and support.

This draft is an inclusive document aimed at alleviating the suffering of RD patients and families in the state through government support and funding. It was submitted to the National Health Mission (Karnataka) on March 1, 2016.[20]

CONCLUSION

This day scenario with respect to orphan drugs among the developed nations is in stark contrast to that in the developing nations like India. The realization that development of orphan drugs would require a different approach as the inherent nature of this endeavor is laced with high costs and fewer returns on the investment, led to the development of various acts in the developed nations. These legislations provided the pharmaceutical companies with the necessary incentives to cause a paradigm shift in their approach toward orphan drugs.

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 bio pharmaceuticals 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.

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