REVIEW ARTICLE

Orphan regulations for orphan drug development in India

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Through this review article an attempt has been made to put forward the challenges faced by rare disease drug development and the current scenario of orphan drug legislations in India. An orphan drug is a pharmaceutical agent that is used to treat a rare medical condition (viz., glioblastoma multiforme, nocardiosis, Tourette syndrome, etc). Developed countries such as United States (US), Europe, Japan, and Australia have laid down legal framework for combating rare diseases. A path breaking legislation was formulated by the US government way back in 1983, known as "Orphan Drugs Act (ODA)." The key purpose of ODA was to incentivize R and D initiatives for such drugs to treat millions of population suffering from "orphan diseases." Though the percentage of patients suffering from "rare diseases" in India is reportedly higher than the world average, unfortunately even today such cases get little help from our government. Indian government should also encourage its domestic pharmaceutical industry to get engaged in research for orphan drugs by putting an "ODA" in place and extending financial support, and regulatory concessions like smaller and shorter clinical trials, without further delay. Thus, India could well-demonstrate that the concept of orphan drugs for orphan diseases is really not orphan in India.

Key words: *Orphan diseases, orphan drugs act, orphan drug*

INTRODUCTION

Diseases that manifest in patient populations representing at the maximum 6-8% of the world population are defined as "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 disease. In United States (US), the Orphan Drugs Act (ODA) is a federal law concerning rare diseases that affect fewer than 200,000 people or are of low prevalence (<7.5/10,000 in the community).[1] A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000). Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan's definition of rare disease. Many of the estimated 5000-8000 rare conditions are genetic or have a genetic component. Others arise from exposure to infectious agents or toxins and occasionally, from adverse responses to therapeutic interventions.

OBJECTIVE

The objective of this review is to look into Indian orphan drug regulations and an emphasis has been laid on ODA of US and orphan drug policies of other developed countries such as Europe, Japan and Australia, thus showing the requirement of adopting ODA like legislation in India.

DISCUSSION

United States took the first step to encourage Pharma Industries in Research of "orphan drugs":

Public awareness drives for "orphan diseases" first originated in the USA with the formation of a rare disease support group representing around 200,000 patients suffering from such diseases. This awareness campaign ultimately culminated into a path breaking legislation in the US named, "ODA", in 1983. The key purpose of ODA was to incentivize initiatives toward development of such drugs to treat around 25 million Americans suffering from "orphan diseases".

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The incentives include:

- Funding towards investigation for "orphan disease" treatment
- Tax credit for clinical research
- Waiver of fees for new drug application
- Offering more lucrative incentive than product patent (product patent requires the drug to be novel), as the orphan designation of the product by the US Food and Drug Administration (FDA) and product approval by them are the only requirements for 7 year market exclusivity of an "orphan drug" for the specified indication
- Market exclusivity of "orphan drugs" become effective from the date of regulatory approval, unlike product patent, product development time remains outside this period
- The drugs, which are not eligible for product patent, may be eligible for market exclusivity as an "orphan drug" by the US-FDA
- Recommendations from FDA staff to sponsors about nonclinical and clinical studies that would support approval of a drug for a rare disease
- Other special assistance, such as accelerated approval or fast track or priority review, may also be available for sponsors of orphan drugs.[2]

Impact of the act

Since the introduction of ODA, nearly 1100 drugs and biological products have been designated as orphan products. The FDA has approved over 231 of these for marketing, thereby facilitating treatment for an estimated 11 million patients in the USA. Also the FDA has so far offered 370 extra mural clinical grants totaling more than $150 million for orphan product developers.

A decade after in 1993, Japan took similar initiative followed by Australia in 1999. Currently, Singapore, South Korea, Canada, and New Zealand are also having their country specific ODA.[2]

India perspective

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.

Figure 1 depicts the future trend of bringing important drugs to patients.

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.

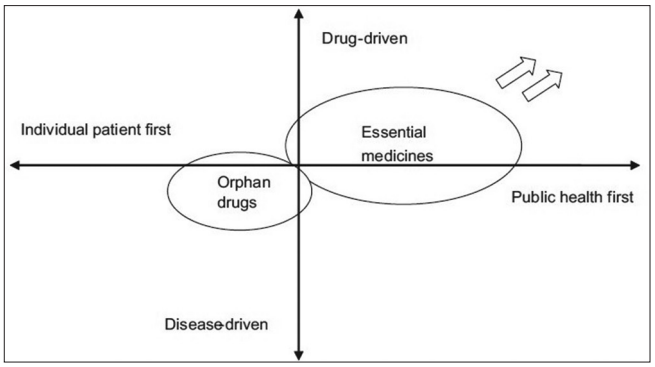

Figure 1: Drug-driven refers to more emphasis on the drug compound for decision-making (e.g., cost-effectiveness, evidence base). "Disease-driven" refers to more emphasis on the characteristics of the disease-making process. The arrows indicate a future trend based on recent developments

As stated above, 1983 signaled the importance of "orphan drugs" with the ODA in the US and later by Japan, EU, and Australia.[3,5] 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 [Table 1].

Every day millions of Indians will continue to suffer from "orphan diseases" without treatment, in the absence of an appropriate policy framework in the country for "orphan drugs".

Challenges faced by orphan drug

The most challenging part in the fight against "orphan diseases" is access to an affordable treatment, especially to affordable "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

Table 1: Comparison of orphan drug policies in various countries

	Comparison of the policies on orphan drugs worldwide			
	USA	**EU**	**Japan**	**Australia**
Legal framework	ODA (1983); orphan drug regulation (1993)	Regulation (CE) no. 141/2000 (2000)	Orphan drug regulation (1993)	Orphan drug policy (1997)
Administrations involved	FDA/OOPD	EMEA/COMP	MHLW/OPSR (orphan drug division)	TGA
Prevalence criterion of the disease for orphan status (per 100,000)	75	50	40	11
Market exclusivity (years)	7	10	10	5 (similar to other drugs)
Funding	Grants for clinical research (pharma and academia eligible)	Framework programmes for research plus national measures	Grants for clinical and nonclinical research (pharma only eligible)	No
Tax credits	50% for clinical costs	Managed by member states	6% of both clinical and nonclinical costs	No
Protocol assistance	Yes	Yes	Yes	Yes
Accelerated review	Yes	Yes (via the centralised procedure)	Yes	Yes
Reconsideration of orphan status	No	Yes (every 6 years)	Yes	Yes (every 12 months)
Application fee waiver	Yes	Reduced fees	No	Yes

ODA: Orphan Drugs Act, FDA: Food and Drug Administration, EMEA: European Medicines Agency, OPSR: Organization for Pharmaceutical Safety and Research, TGA: Therapeutic Goods Administration, USA: United States of America, EU: Europe, COMP: Committee for Orphan Medicinal Products, OOPD: Office of Orphan Products Development, MHLW: Ministry of Health, Labour and Welfare

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. Indian patients suffering from rare diseases will currently have no other alternative but to import these drugs directly in US$ term, unless Indian policy makers wake-up some day and take appropriate measures in this important area.[2,4]

"Orphan Drugs Act" must come with adequate incentives

Orphan Drugs Act, when enacted in India, should not be a half-hearted approach or be a zero-sum game for all. It should come with adequate financial and other incentives to create a sound business sense in this new ball game for the pharmaceutical players in India. The government should keep an eye on the challenges faced by orphan drugs and take proper measures before enactment of legislation.

CONCLUSION

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.

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